ANNALS OF
INTERNAL MEDICINE

VOLUME 12 AUGUST, 1938 NUMBER 2

A CONSIDERATION OF THE ACQUIRED RESISTANCE OF FIXED TISSUE CELLS TO INJURY *

By WM. DEB. MACNIDER, M.D., F.A.C.P., *Chapel Hill, North Carolina*

ONE of the many pleasant experiences that come to a person who has lived for years a laboratory type of life, one interested in investigation and especially if such study has had a certain continuity of purpose, is that an opportunity presents itself to review this work, to see it in a measure as a whole and as Bacon suggested, to catch the resemblances of things, one to another, which he considered was the main point in acquiring information which partook of understanding. Through an analysis of such resemblances one may be able with a caution to come to a composite type of conclusion in which experiments differing much in their initial purpose or even in their major objective tend to focus to a common point and shed light not only on a meticulous part of a problem but on such related problems that a principle may evolve based on reason dependent upon experimentation.

For nearly 30 years experiments have been in progress in this laboratory which have been primarily concerned with both the type of tissue reaction and the functional expression of such a reaction which develops in two organs, the kidney and the liver, when these organs are subjected to injury by certain mechanical manipulations or the action of a variety of chemical poisons. When chemical bodies were employed, they were selected in the hope of either injuring such organs in a diffuse manner or localizing their injurious influence to some particular part or structure in the organ. Injury to tissue associated with the survival of the organism participating in the injury, connotes the development of some type of repair process which enables the animal to make or to fail to make an organ adjustment both within the injured organ and also with such a repaired organ related to other structures in order that through such an adjusted state the animal may again participate in the life process. The order of this life process in terms of both function and resistance to subsequent injury depends upon

* An address delivered at the Twenty-second Annual Session of The American College of Physicians, New York City, April 7, 1938.

From the laboratory of pharmacology, The University of North Carolina.

the type of cell effecting the repair. A repair by a baser, supporting tissue for highly specialized cells with a specific type of function results in an acquired resistance with an absence of functional adaptation. A repair by an altered type of cell resembling the cells which have degenerated may restore function to a certain level of pathological effectiveness and at the same time impart to such a repair process a degree of resistance to secondary injuries. Tissue repair when considered as a tissue adjustment with function is effected by tissue changes which fall into two categories of cytological reactions: cell recuperation or cell regeneration. In the former process of cell recuperation, cytoplasmic and nuclear readjustments occur which bring the injured tissue back to its cytological normal. It becomes of normal, functional value and shows the usual degree of susceptibility to injury. In the higher animals very little is known concerning this type of repair process. The give and take of highly specialized cells in the normal and, especially, in the pathological life process, injury, recuperation, with a transitory adjustment to an organ and organism environment are states which deserve extensive study and which will not be understood by waiting for the autopsy table to reveal a terminal event, death. Death dependent upon progressive changes of degeneration must be preceded during the life span by both chemical and morphological changes in cells, indicative of their elasticity, which make cellular adaptations possible. In addition to tissue reactions characterized by cellular recuperation, there is a second type of cell change, regeneration, which may develop as a repair process when a sufficient degree of injury has been inflicted that results in the formation of a normal type of cell of the usual functional value, or the cytological injury may be of such an order that a normal type of cell can not be formed. The severity of the tissue injury and the age of the animal in which such an injury takes place influence the type of functional cell which is formed. There may appear through a process of regeneration an abnormal, atypical form of cell with modified function and such cells may have acquired a resistance not only to the cause of the injury but to other agents of a harmful nature. A cell metaplasia has developed as a response to an injury which enables an organ to function and function perhaps at a lower level of effectiveness; yet, associated with the change in cell type, a resistance to injury has developed. It is this latter type of cell repair, a repair not of recuperation but one characterized by the formation of new cells, with which this discussion will be concerned. Here again it would appear worth while to emphasize the fact that cellular repair as regeneration may not take place by the formation of a normal type of cell. Such cells of repair under certain conditions appear to be unable to reappear as a normal order of cell for a given tissue location but, as a result of tissue reactions dependent upon injury, the ultimate nature of which is unknown, offer as a substitute cells of a changed type, certainly differing morphologically and presumably chemically from the normal cell. The development of such changes in cell form following a tissue injury may only constitute a transitory departure from the normal. In some instances

there appears to be an inherent tendency on the part of such atypical cells of repair to revert to a cell of normal configuration for a given tissue location. Such shifts in cell type have a place in any fundamental understanding of disease states. Their appearance upsets our conception of tissue repair invariably developing true to cell form for a given organ location and forces us to consider not only the cause, severity of injury, and age of the animal in which such cell reactions occur but in addition, the changed environmental state due to injury in which such a repair process has been able to develop and in which it must relate itself and persist. A repair process characterized by modification in cell form with function and with an acquired resistance may not be disease with an end reaction of death but life of a modified order with a transitory period of acquired protection.

Many years ago certain studies [1, 2, 3] were undertaken to ascertain the type and extent of the injury which developed in the kidney of the cat when one branch of the renal artery was occluded by ligature. These studies were furthermore instituted in order to observe the processes of repair which might appear in such large areas of renal injury in which an adequate vascularization of the injured tissue had developed. Ligature of one of the main branches of the renal artery in the cat leads to the development of a large area of necrosis, the size of which depends upon which branch of the artery has been occluded. The central portion of such an area becomes completely necrotic and later undergoes a shrinkage. Connective tissue cells invade the greater portion of such areas while at their margins there occurs an ingrowth of blood vessels which is followed by a modified type of repair process. In many areas in such zones of injury the ingrowth of vessels is sufficient to permit an atypical type of epithelial repair process to develop in the region of the convoluted segment of the tubule. Such a process of epithelial repair in these areas of injury does not take place by the formation of normal cuboidal cells specialized in their internal structure but by the formation of a very flattened type of epithelium which either shows imperfect cell differentiation or occurs as undifferentiated syncytial structures. Nothing is known concerning the function, if any, of tubules lined by this type of epithelium. The relined tubules appear to end blindly and have between them a capillary network which is adequate as a source of nutrition to maintain the physical integrity of such an atypical epithelium. It would appear that in such zones of injury an altered organ environment has been established by restricting its blood supply to which a normal type of specialized epithelial cell is unable to effect its adjustment but that with a blood supply adequate to maintain in some measure epithelial life, a process of epithelial repair is accomplished of a modified order, which epithelium is resistant and can adjust itself to the altered renal environment in which it makes its appearance. An epithelial adjustment has been made to an altered environmental status of an organ. Such a conception carries with it the assumption that the altered type of epithelium is of a resistant form and

that such an acquired resistance enables such cells to persist in areas which are unfavorable for the life of a normal type of cell.

A similar type of cell adjustment likely occurs in various organs which have been subjected to a sufficient degree of injury. It would appear to be especially common in the convoluted segment of the tubule in both epithelial and vascular types of nephritis, especially the latter. In such a form of renal injury, progressive arterial and glomerular damage leads ultimately to such a change in the blood supply of the kidney that a normal type of epithelial cell is unable to persist in this segment of the tubule. In its place are found atypical, flattened cells, frequently in syncytial configuration which are usually spoken of as cells of atrophy, flattened by pressure from within the tubule. Such a conception may or may not be correct. However, from an experimental point of view the more natural inference would be that such flattened cells represent an atypical type of epithelial repair which has been made necessary on account of a normal type of cell being unable to adjust itself to, live and function in, a renal environment so extensively modified by changes in its blood supply. Changes in epithelial type of a similar nature have been observed in the kidney of senile individuals and have been attributed by Kaufman [4] to the aging process. Epithelial repair processes of the order under discussion may be a part of a mechanism which not only tends through the resistance of such cells to transitorily stabilize a chronic nephritic with a certain degree of renal function but for a period to afford some degree of acquired renal resistance to injury. Such an interpretation of changes in cellular morphology enables one to see such changes not solely in terms of degeneration, but as shifts in cell type in given organ locations in order to effect an adaptation to a changed organ environment occurring either as a result of disease or as a part of physiological senescence. Cellular changes of such an order may result in lessened function, life at a lower level of effectiveness and yet afford a certain degree of protection to injury for periods variable in their duration. With such a conception of the significance of cell changes during the life span of an organism and developing as a process of repair secondary to injury, it becomes rather difficult to decide just what cellular events should be embraced by the term disease.

As a result of the interest developing from these early and simple experiments on tissue repair which have been referred to, work of a different experimental nature has been in progress in this laboratory for some years in which various chemical substances, especially the salts of uranium, have been used to effect an injury to either the kidney or the liver. During the period of such acute injuries and later when processes of repair were in progress, these organs have been studied histologically by the removal of biopsy material and by various tests which would give some indication of the functional value of such organs during the acute injury and at various stages of the process of repair. In addition to such observations, especially when uranium was used as the nephrotoxic or hepatotoxic agent, the animals have

been reintoxicated and subjected to both histological and functional studies in order to ascertain not only the state of function of such organs but to determine whether or not a state of increased susceptibility or one of acquired resistance had developed in the liver or the kidney as a result of the type of repair process which had been instituted from the initial acute injury.[5, 6]

The fact has been known since the early work of Chittenden and Hutchinson [7] that uranium salts have an affinity for the epithelial tissue of both the liver and the kidney. Suzuki [8] was inclined to specifically localize this injury to a particular segment of the convoluted tubule. The injury is selective in this location in that it develops here as the earliest manifestation of the intoxication, but other tissues of the kidney, the glomeruli, are also injured as is shown not so much by acute changes but by the process of repair in these structures which finally advance to such a state of chronic degenerative injury as to constitute a chronic, vascular type of nephritis.

The ease with which both the acute and chronic changes can be induced in the kidney by uranium is in a measure determined by the age of the animal. Young animals show an epithelial resistance to this substance. The epithelial repair process in such an age group is usually characterized by the formation of a normal type of epithelial cell. Fibrosis and hyalinization of the glomeruli occur less readily in young animals than in adult animals. In contrast to the reaction of puppies and young animals to uranium, adult animals and certain senile animals show an increased susceptibility to both the epithelial and glomerular damage which may be inflicted by this poison. This variable, the factor of age, has to be taken into consideration not only in studying the severity of the acute injury but also in gaining information concerning the type of repair process which develops, especially in the epithelium.[9, 10] An understanding of the way in which the age factor influences epithelial susceptibility to injury and the type of epithelial cell repair, as well as the changes in the glomeruli, is difficult to ascertain, for there is but little accurate knowledge of what actually constitutes aging on the part of tissues. The severity of the epithelial injury certainly reflects itself in the type of repair process which is instituted by such tissue. This factor fails to operate in terms of the changes of repair induced in the glomeruli. Histologically, acute glomerular injuries of the same order of severity are followed by processes of repair which are essentially different in terms of the degree and completeness of chronic, glomerular degeneration. In puppies and young animals the glomerular injury is followed by an order of change which should be looked upon as a change of recuperation. In general the glomeruli return, following an acute injury to structures which are histologically normal. When these bodies are injured in adult and especially in senile animals, there occurs as a reaction of repair the formation of both capsular and intercapillary connective tissue which later undergoes hyalinization leaving the glomeruli for a period canalized, rather than capillary structures. From these observations it

would appear that the age of an organism such as the dog very largely determines the period in the life span of the animal at which connective tissue formation most readily develops in the glomeruli.

In the following account of those changes of both injury and repair which develop in the kidney and the liver during the course of intoxications by uranium nitrate, the factor of age, on account of its significant influence, will be given adequate consideration.

When young dogs are intoxicated by 2 to 4 mg. of uranium nitrate per kilogram of body weight, the first evidence of renal injury which can be histologically demonstrated occurs in the convoluted tubule cells. Such cells show a deposition of stainable lipoid material, cloudy swelling with edema and partial necrosis. The degree of necrosis is variable. No attempt will be made to interpret the functional expression of such an injury for in the higher animals tubular function, whatever it consists in, can only be separated from glomerular activity by inference. The repair process which develops in this location of the renal tubule in young animals from such a degree of injury is characterized by the formation of a normal, cuboidal type of cell, specialized in its internal structure, which, functioning in association with glomeruli that appear uninjured, restores the kidney to its normal functional value. With the completion of such a process of repair if these animals be given a second subcutaneous injection of the same amount of uranium nitrate per kilogram, the specialized cells which have effected the epithelial repair fail to show any evidence of an acquired resistance. An acute epithelial injury develops which may be of a severer order than the initial injury. A greater degree of necrosis occurs and lipoid material in an increased amount appears in such damaged cells. Such secondarily intoxicated animals frequently fail to survive. Their death is of a renal type associated with the development of a marked disturbance in the acid-base equilibrium of the blood which at its commencement is out of proportion to the degree of renal injury as indicated by the various tests employed to ascertain renal function. These experiments indicate that when young animals are intoxicated by uranium nitrate an injury to convoluted tubule cells is induced which is not of a severe type. The repair process results in the formation of an epithelial cell of normal configuration which manifests no acquired resistance to secondary uranium intoxications. In certain of the animals these cells of repair are more susceptible to uranium injury than are the normal cells in this segment of the tubule.

The influence of the age factor in determining cell susceptibility and to an extent the type of cell repair is not only of general biological interest but assumes significance of a biological nature as applied to medical problems. Observations which are to follow indicate that in older animals the usual type of cell repair to convoluted tubule epithelium is by the formation of not only an atypical cell for this segment of the tubule but one which also is resistant to injury. Such modifications in cell structure as a reaction to injury may be a factor in deferring organ and organism senescence.[11, 12]

The same factor may be operative to an extent in determining the type of disease process likely to develop at various age periods.

The reaction of renal tissue of older animals to an intoxication by uranium nitrate is not only more severe but of a more diffuse nature than is the case with younger animals. The earliest evidence of injury in these animals is also expressed by processes of degeneration in the epithelium of the convoluted tubules. The epithelial injury is not confined to these cells but shows itself in the loops of Henle, especially the ascending limb, by a marked deposition of stainable lipoid material. Furthermore, in animals of such an age group, regardless of whether the glomeruli show more evidence of acute injury than occurs in the younger animals, there develops an early and progressive connective tissue reaction in these structures, finally leading to their partial or complete obliteration as capillary bodies. In animals of such an adult or older age period the injury to the convoluted tubule cells is associated with the formation of lipoid material as droplets or fused masses, edema and cell vacuolation terminating in a state of necrosis which is variable in its degree of completeness. Not infrequently in such cells the seat of severe damage, the nuclei stain well and appear in a fair state of preservation. A considerable number of animals showing such a degree of renal injury fail to survive the intoxication. Those effecting a survival institute a repair process to the damaged epithelial tissue which results in the formation of an entirely different order of cell for this segment of the nephron. Such cells are invariably flattened which in turn increases the diameter of the tubule. This increase in size of the tubular lumen is not due to the compression of a normal type of cell. It is due to a change in the morphology of the cells which line the convoluted segment and which make their appearance as a process of repair. Such a statement can only be made by a study of biopsy material during the period of repair. Understanding of such cellular events can never be obtained solely by autopsy observation. Death and the dead house eliminate the sequence of events as pathological life which finally expresses itself at the autopsy table. In addition to the flatness of these newly-formed cells of an atypical order which appear in the convoluted tubules as a reaction to a severe injury in an animal of an appropriate age period, the cells usually possess large, deeply staining nuclei and show imperfect cell differentiation. In other areas this segment of the nephron becomes lined by undifferentiated epithelial tissue in definite syncytial formation. In these structures the nuclei are irregularly placed. The origin of these atypical cells of repair is two-fold. In convoluted tubule segments the epithelium of which shows complete necrosis an attempt at repair, which has never been observed to be completed, may arise as a result of an ingrowth of cells from the descending limb of Henle's loop into the necrotic material which may remain in the convoluted segment. The usual mode of repair which reaches a state of completion is from the cells of the convoluted segment which have not participated in such a degree of injury as to make nuclear division and cytoplasm formation impossible.

Such a repair process does not take place uniformly throughout the damaged tubular segment but occurs in isolated areas. From such nests of regenerating epithelium the tubule becomes relined by a continuous epithelial layer either as a syncytium or as imperfectly differentiated, flattened, cell masses. A repair with an epithelium of an embryonic type has developed in animals of this age period following a sufficient degree of epithelial injury. It would appear that the degree of injury inflicted to such specialized cells is of great importance. A slight injury is insufficient to so change the constitution of cells as to prevent them from instituting a normal type of cell repair. With a severe injury to the same type of cell, especially if the injury takes place in an adult or senescent animal, an atypical form of cell appears as a repair process which has certain of the characteristics of embryonic tissue. Such an atypical type of cell repair affords protection to this formerly susceptible segment of the tubule as is shown by the fact that such cells are resistant to uranium nitrate intoxications when this nephrotoxic agent is used in an amount in excess of that necessary to induce a severe necrosis of normal cells.[13] An observation of a similar nature has been made when animals which have shown an acquired epithelial resistance to uranium are intoxicated by bichloride of mercury. This poison selectively injures in a normal animal the epithelium of the convoluted tubules. If the epithelium in this location of the tubule has changed its type as a result of a process of repair to an acute uranium injury, it has been found to have also acquired a resistance to bichloride of mercury. During such periods of epithelial resistance to both uranium nitrate and bichloride of mercury these nephrotoxic substances can be demonstrated in the urine.[14]

The experiments with uranium nitrate which have been briefly outlined indicate that a slight injury to the convoluted tubule cells from this substance is followed by a repair process which results in the formation of a normal type of cell both in its general morphology and in its internal structure. Cells of this order have failed to manifest any resistance to secondary intoxications by uranium. In other animals, especially those falling in an adult or senescent group, the use of this poison induces a severer type of tubular injury which is followed by a process of epithelial repair in which the cells are of an atypical type without specialization in their internal structure and which have certain characteristics of embryonic tissue. A repair of specialized, damaged epithelium by this order of cell imparts to the segment of the nephron in which it develops not only an acquired resistance to the nephrotoxic agent which induced the acute injury but to an injurious agent, bichloride of mercury, which specifically acts on that part of the tubule which has participated in the atypical type of epithelial repair. These experiments not only demonstrate an acquired resistance of the epithelial cells of repair to uranium and bichloride but in addition the observation is made that such cells are able to adapt themselves to those chronic changes of a vascular nature which develop in the kidney as a delayed but essential part of the uranium injury and which, when taken in conjunction with the

epithelial changes, constitute a chronic nephritis. The atypical cells of epithelial repair manifest three forms of resistance: a resistance to the substance which provoked their formation, a resistance to another type of certainly acting chemical poison, bichloride of mercury, and finally to a severely altered renal environment established by changes of degeneration in the glomeruli.

In experiments on the kidney in which the higher animals are used, it is impossible to evaluate except by inference, which may be very misleading, the degree of function which should be ascribed to such intimately interrelated structures as the glomeruli and the renal tubule. Even when nephrotoxic substances are used which have a selective affinity for renal epithelium it becomes impossible to ascribe departures in renal function to such an injury. Furthermore, when different types of epithelial repair processes develop in such tissue which may or may not have acquired a resistance to injury, it also becomes impossible to know whether or not such types of epithelium are of functional value. Such information is necessary in order to evaluate the significance of an epithelial repair. If such an epithelium is of no functional value, this type of repair which imparts resistance is useless to the organ in which it occurs and therefore to the organism as a whole. On the other hand, if the resistant type of epithelium, even though changed in its configuration and internal structure, possesses function of a normal type, then a tissue reaction has developed through a process of repair which enables organ survival as a functional entity and through such organ resistance a contribution is made to the survival of the individual.

In order to ascertain whether or not an organ, in which an atypical type of epithelial repair had developed which imparted resistance, was associated with function of a normal order, the liver has been chosen for investigation on account of the lack of dependency in this organ of the function of its epithelium on any other structure. In these experiments hepatic function has been estimated by determining the initial plasma concentration of phenoltetrachlorphthalein and the rate with which the dye is removed from the plasma by the normal liver, the liver the seat of an acute injury from uranium nitrate, and at periods of repair when such processes had been effected by the formation of both normal and atypical types of epithelial cells. This test gives little information in terms of relative quantitative values. It indicates the development of gross injuries to liver epithelium and in addition its use is of sufficient value to determine whether or not an atypical type of epithelial repair is of functional value and to a less extent the degree of function possessed by such a repair process.

In the experiments which are to be reviewed, the same observation has been made in connection with the susceptibility of the normal liver to injury as has been made for the kidney. In general, regardless of the weight of the animal and therefore the total amount of uranium received, this substance induces less evidence of epithelial injury to the livers of young

animals than it does to those of adult animals and the usual senile animal in which no change in this tissue has developed as a part of the senile state.

An intoxication by uranium nitrate in the amount of 2 to 4 mg. per kilogram of body weight is followed by an injury to the liver which consists in fatty infiltration of the epithelium, edema and cell vacuolation with scattered areas of necrosis. A diffuse liver injury of such an order is usually indicated by a slight increase in the initial plasma concentration of phenoltetrachlorphthalein and by some delay in its removal from the plasma. An injury of such a degree is followed by a process of repair which results in the formation of a normal type of polygonal epithelial cell which is of normal functional value. When such animals are reintoxicated by the same amount of uranium nitrate per kilogram, a secondary injury which may be of a severer nature than the initial injury develops and associated with it there is an increase above the normal value in the percentage concentration of phenoltetrachlorphthalein and a delay in the removal of the dye from the plasma. The repair process which has been accomplished by the formation of a normal type of cell has no acquired resistance to a secondary intoxication by this hepatotoxic substance. In other animals intoxicated by the same amount of uranium nitrate per kilogram a severer type of hepatic injury develops. This is more apt to occur in adult animals over six years of age. This order of injury as shown by a study of biopsy material consists in a marked accumulation in the epithelium of stainable lipoid material, edema of the cells and a more diffuse though not complete state of necrosis than that which occurs in those animals of the former group which have been described. With such a degree of epithelial injury the plasma concentration of phenoltetrachlorphthalein reaches a high level and the rate of its removal is proportionately delayed. A number of the animals with such a degree of hepatic injury fail to survive. Those effecting a survival repair the liver by the formation of an epithelium which is essentially different in its morphology from the normal polyhedral type of cell. Such a repair process originates in areas of severe liver damage characterized by a partial necrosis in which islands of hepatic tissue persist which are insufficiently injured to prevent the development of a process of repair. In such areas this process develops in a two-fold manner. The injured and ill defined cellular masses may increase in size through nuclear division and cell cytoplasm formation and remain as a syncytial mass from which buds develop and cord-like, imperfectly differentiated, epithelial structures grow into the general area of necrosis. In other locations there arise from injured epithelial tissue without the formation of a primary syncytial mass, cord-like structures which invade areas of epithelial necrosis in an irregular manner, though usually tending to converge towards the central vein of the lobules. This newly formed epithelium of repair is of a flattened type of cell structure which either shows imperfect cell differentiation or persists in syncytial formation. From such structures branching and budding of the epithelium may be observed with, not infrequently, bridges of nucleated epithelial

tissue connecting parallel cords of flattened liver cells. Between such cords of cells or syncytia are found greatly enlarged venous sinusoids.

The liver, the seat of such an abnormal type of epithelial repair process, retains its ability to remove phenoltetrachlorphthalein from the plasma. The initial plasma concentration of the dye is greater than occurs in animals with a normal type of epithelial repair and the rate with which the dye is removed is prolonged. When animals that have effected a repair to the liver by the formation of an atypical epithelium of this order are reintoxicated with uranium nitrate in an amount in excess of that which induced a severe injury to normal hepatic epithelium, the abnormal type of cell is found to be resistant to this hepatotoxic agent as is shown by the failure of the cells to become severely injured or necrotic and by the maintenance of hepatic function as indicated by the ability of such cells to remove phenoltetrachlorphthalein from the plasma.

The reaction of the liver in terms of cell repair and acquired resistance is similar to that of the kidney as was indicated by such changes in the cells of the proximal convoluted tubule. A slight injury to such epithelial tissues is followed by a normal type of cell repair which has no acquired resistance. A severe injury prevents the normal type of repair process, the repair being accomplished by an atypical cell or by structures in syncytial formation which in the liver may be ascertained to be of functional value.

These observations would appear to have certain significant implications for they indicate that when an adult and differentiated tissue is so disturbed through injury that a normal type of cell repair becomes impossible, a repair process resulting in the formation of an embryonic type of tissue develops which not only acquires a resistance to injury greater than differentiated tissue but retains to a certain degree its normal functional value. Such an observation furthermore raises the question as to whether or not a sufficient degree of cellular injury can precipitate a type of cell repair which should be looked upon as a structural reversion of an ontogenetic order.

With the demonstration that following a uranium injury of a sufficient degree of severity a type of epithelial repair would develop which afforded resistance from secondary injuries from the same poison, the question naturally arose as to whether or not such an acquired resistance was specific or whether it was effective for other chemical agents with a demonstrated toxicity for hepatic epithelium. Many years ago it was shown by Whipple and Sperry [16] that if a dog was starved for 24 hours and given chloroform by inhalation for one and one-half hours, there invariably developed a necrosis of the hepatic lobules involving one-half to two-thirds of their area. The following group of experiments have been conducted, with the above observations in mind, in order to ascertain if an atypical type of epithelial repair induced in the liver by a severe injury from uranium would afford the liver protection against the certainly acting hepatotoxic agent, chloroform, when given to animals under the standard conditions as outlined by Whipple and Sperry. A group of young dogs were intoxicated

with 2 to 4 mg. of uranium nitrate per kilogram. In such animals, as has been recorded, there develops a diffuse injury to the epithelium in which necrosis is not marked and which is characterized by fatty infiltration, granular degeneration and edema of the cells. There occurs a slight increase in the initial plasma concentration of phenoltetrachlorphthalein and usually some delay in the removal of the dye from the plasma. An injury of such an order of severity in young animals or puppies is followed by the development of a repair process which restores the liver to its normal structure. The epithelial repair is by a polyhedral type of cell. Such a process is completed within two weeks with a return of the liver to its normal functional value. When animals with this type of epithelial repair are starved for 24 hours and given chloroform by inhalation for one and one-half hours, there occurs a necrosis associated with fatty degeneration of the inner one-third to two-thirds of the hepatic lobules. The ability of the liver the seat of such an injury to remove phenoltetrachlorphthalein is definitely decreased.

When older animals are intoxicated by the same amount of uranium nitrate per kilogram or by an amount in excess of 4 mg. per kilogram, there develops a severe and diffuse injury to the liver lobules in which epithelial necrosis is the most marked pathological characteristic. The epithelial repair process when it occurs following such a degree of injury, results in the formation of the usual atypical, flattened cells or of an epithelium syncytial in structure. The liver with this type of completed repair may have a normal functional value as shown by the use of phenoltetrachlorphthalein. When such animals are starved for 24 hours and given chloroform by inhalation for one and one-half hours, there fails to develop the characteristic central necrosis of the liver lobules. A fixed cell tissue resistance has been acquired on the part of atypical hepatic epithelium developing as a repair process to a severe injury from uranium nitrate, which has not only been shown by previous experiments to have a resistance for uranium, but also by these experiments to an entirely different chemical body, chloroform. Such an observation might warrant the assumption for the acquired resistance that the atypical cells of hepatic repair were unable to subject themselves to the action of chloroform in sufficient concentration to effect an injury. Even if this were true, such cells should be considered resistant if they maintained hepatic function. Such function is maintained by these cells as is indicated by their ability to regulate the plasma concentration of phenoltetrachlorphthalein and remove the dye from the plasma. Two factors apparently determine the degree of acquired resistance of such a type of repair process to chloroform: the duration of the preliminary period of starvation and either the concentration of chloroform in the liver or the length of time to which hepatic tissue is subjected to its action. If animals which have been starved for 24 hours and given chloroform for one and one-half hours with the demonstration of a complete hepatic resistance, be later starved for 48 hours and given chloroform for three hours, a commencing

epithelial necrosis develops in the cells which have previously shown resistance in the location in the lobule where it should develop, centrally, around the central veins of the lobules. An acquired, fixed tissue cell resistance, like other forms of resistance, is relative and not absolute.[17]

Extending over a period of 14 years, a large number of animals have been used in this laboratory in which the liver was either primarily the object of investigation or in which it was subjected to study in conjunction with other organs and tissues. A rather large number of dogs have been observed which, on the basis of their age and certain associated physical defects, may be classified as senile animals. Such animals have varied in age from eight years to fifteen years and four months. Occurring in such a group of animals there has been found, at autopsy or by the removal of biopsy material, 26 dogs in which the liver has shown a diffuse change in its type of epithelium. The changes in these cells which have resulted in an altered structure of the liver resemble very closely those changes which may be induced experimentally by subjecting the liver to a severe intoxication by uranium nitrate which results in the development of an atypical type of epithelial repair. In these senile animals the epithelium shows very little evidence of cell differentiation but exists in the form of intensely staining syncytial cords, the irregularly placed nuclei of which are large in proportion to the surrounding cytoplasm and also stain deeply. Such cords are uniformly narrow and exhibit both branching and budding. More rarely, such structures end blindly by bifurcating into two cords of nucleated cytoplasm. Between such structures are to be found greatly enlarged venous sinusoids. These cords of epithelium are bizarre in their arrangement and fail to converge with any regularity toward the central veins of the lobule. When senile animals, that have been shown by a study of biopsy material to have an altered epithelial structure of the type described, are starved for 24 hours and given chloroform by inhalation for one and one-half hours, there fails to develop any evidence of cytological injury to such altered epithelium. The functional value of these cells, which may closely approach that of normal hepatic epithelium, fails to show any change in the rate with which it disposes of phenoltetrachlorphthalein. The cause for the formation of this atypical type of epithelium in the livers of senile animals is unknown. It has only been observed as a naturally acquired type of cell change in senile animals. In such senile dogs, similarly to those dogs in which this form of epithelium appeared as a repair process secondary to a severe hepatic injury, the embryonic, imperfectly differentiated, or clearly syncytial character of the epithelium appears to impart to this tissue resistance, while at the same time it retains its functional value in so far as one test for hepatic function is concerned. In the senile animals as was the case with the group of animals formerly described, the resistance to chloroform is not of an absolute value. If senile dogs which have shown resistance to chloroform as has been indicated above, be starved for a longer period and the duration of the chloroform anesthesia be increased, there develops evidence of epithelial

injury around the central veins of the lobules. Usually from such a degree of injury there is no change either in the initial plasma concentration of phenoltetrachlorphthalein or in the rate with which it is removed from the plasma.[18]

The question very naturally arises as to whether or not such cell metaplasias, which may be made to develop in the liver and the kidney as the result of injury and which may occur in the senile liver from some unknown cause and which show an acquired resistance, are permanent, or whether such cells may revert back to a normal type. This question can only be answered for a group of animals in which the liver was severely injured by uranium nitrate with the formation during repair of an atypical epithelium. At intervals after this type of cell was demonstrated to have appeared, histological studies of the liver were continued over several years by obtaining biopsy material which enabled any change in cell type to be observed. During these years of observation the animals were either reintoxicated by uranium or after a period of starvation subjected to the action of chloroform. In this relatively small group of animals the observation has been made that after periods which vary from a few months to approximately two years, the atypical, flattened type of resistant cell and in areas the syncytial structures show a reversion to a normal polyhedral type of cell. The rate with which such changes in cell reversion take place appears to depend on the age of the animal, occurring more rapidly in young animals than in adult and senescent groups. When animals which have shown such a partial reversion in cell type to or towards a normal order of polyhedral cell are starved and anesthetized with chloroform, such areas of cell reversion which are irregular in their distribution in the liver lobules give evidence of a loss in their acquired resistance in that changes of fatty degeneration appear in such cells followed by partial or complete necrosis. Three senile animals that have shown in the liver a change in epithelial type with an associated acquired resistance have been studied at intervals of three months over a period of eighteen months. During this time no indication of a reversion of these atypical cells to a normal type of cell has been observed.[19]

Summary

A review of the experimental work which has been presented in this discussion may with caution allow certain generalizations.

A sufficient degree of injury to specialized cells is usually followed by the formation of a functionally inactive tissue which though resistant to injury is of no value to organ function or the organism as a whole. A survey of different types of experimental procedures which have been employed in this investigation and which have extended over a period of years would indicate that for two organs, the liver and the kidney, a repair process may develop in their epithelial structure which is significant in that an altered, atypical type of cell is formed which is not only of functional

value but which is resistant to a changed organ environment in which it has to live and which is furthermore resistant to extraneous agents of a chemical character, certainly toxic for a normal type of cell. At present we have no method of such selectivity in its application that it will determine the functional value of resistant cells when they appear in the kidney as a reaction of repair. The function of such structure is so intimately related to glomerular function that a separation in the functional value of the two tissues becomes impossible. On the basis of experimental data, kidneys in which such an epithelial process has developed, associated with chronic glomerular damage, may have for months very slight interference in function and at the same time show a definite resistance to injury. The processes of repair resulting in such an acquired cellular resistance would appear to stabilize, for longer or shorter periods, renal function at a given pathological level of effectiveness and at the same time afford the kidney a certain degree of protection. Such tissue reactions would therefore be looked upon not as essentially degenerative and in this sense of no value, but as reactions which preserve a certain degree of function and at the same time impart resistance.

The studies of injury and repair which have been outlined in some detail for the liver on account of the structure of this organ, permit an evaluation of the degree of function possessed by the liver when different types of epithelial repair develop. These studies indicate that an abnormal type of epithelial cell may develop as a repair process, following a severe injury from uranium nitrate, which is not only resistant to uranium when used in an amount in excess of that necessary to injure normal epithelium but that such cells are also resistant to an entirely different substance, chloroform. This metaplastic epithelium of repair is of definite functional value and may even be of normal functional effectiveness as is shown by its ability to regulate the degree of concentration of phenoltetrachlorphthalein in the plasma and the rate with which this substance is removed from the plasma. The same type of statement may be made for the atypical epithelium which is found to occur naturally in the livers of certain senile animals. It is realized that these observations concerning an acquired, fixed cell resistance which may follow tissue injury and which have been observed to occur in senile animals are of a superficial nature. It is not inferred that a mere change in cell form is responsible for such states of acquired resistance. The assumption is made that associated with such changes in cell morphology, the finer, intracellular structure of such cells must be so changed and likely their chemical nature so modified that when they are subjected to a toxic agent in sufficient concentration to injure normal cells, such atypical cells either remain entirely resistant or their resistance is much greater than the normal order of cell which they have replaced. This inference is strengthened by the fact that when resistant, metaplastic cells revert to cells of normal configuration and acquire spe-

cialization in their internal structure, their ability to resist injury decreases or is lost.

The atypical, flattened form of cell which has been described as offering in both the liver and the kidney resistance, is usually dispensed with by the assumption that such cellular modifications are an expression of cell atrophy and therefore represent a retrogressive change tending towards imperfect function, a lack of resistance and, ultimately, to an arrest in function in organ death. Such a conception of the significance of the cell types under consideration is entirely inadequate. It becomes difficult to conceive of atrophy, as such a state is usually interpreted, as occurring with new cell formation which is the case in the cell metaplasias under discussion. Atrophy as cell retrogression and degeneration develops in fixed cells from a variety of causes usually having a nutritional basis or as a pressure effect, and is essentially concerned at first with a modification in the configuration of existing cells and does not include in such a process new cell formation. Furthermore, the cell of atrophy is in general characterized by a definite diminution in function or the development of a functionless state, such states being associated with increased susceptibility to injury. The type of fixed cell of repair which has been the subject of discussion may be of normal functional value and yet manifest a definite resistance to injurious agents. Cells with such characteristics maintain life and should not be considered as primarily participating in a process which leads to organ dysfunction and death.

Of recent years, studies of the acquired resistance of tissues to injury have established certain facts which should be recorded in connection with the observations which have formed the basis for the present study. In 1927, Weller,[20] in his studies of the tolerance to lead as shown by the meningocerebral manifestations of acute and subacute lead poisoning, came to the conclusion that an actual, acquired tolerance to this metal developed in the guinea pig on the part of such tissues. Very recently Sprunt,[21] in a study of "Simple Atrophy of the Liver" in human material, has observed the development of the same type of altered, metaplastic cell which has been described as occurring in the liver of dogs as a reaction of repair and in certain senile animals. He states that "although the conclusions drawn in this paper are based on an analogy between certain morphological changes in the human liver and those in the dog, it is believed that further study will show that these changes in man are, as they are in the dog, associated with a changed physiological response." Observations of a somewhat similar nature on the acquired resistance of fixed tissue cells to injury have been made by Hunter [22] who was able to induce in rabbits a resistance to bichloride of mercury following an injury from this substance which resulted in the development of an atypical repair process to the tubular epithelium of the kidney and by Smyth, Smyth and Carpenter [23] who observed an acquired resistance on the part of hepatic epithelium to carbon tetrachloride when used for purposes of secondary intoxication. Prior to the observation of

Hunter on the acquired resistance of renal epithelium to bichloride of mercury, Havill, Lichty, Taylor and Whipple,[24] in a study of the disposition of hemoglobin by the dog kidney, observed in certain of their animals that had been given hemoglobin close to the renal threshold value with the accumulation of pigment granules in the epithelial cells of the convoluted tubules that such dogs would tolerate the normal minimal lethal dose of bichloride of mercury with little if any evidence of injury to the tubular epithelium. Very recently Olitsky, Sabin and Cox [25] have observed that young mice are more susceptible than older ones to a nasal inoculation by a specific virus and furthermore that this difference was not due to the presence of antibodies in the older mice as such animals were not immune to intracerebral inoculation. The point of resistance or blockage to the invasion of the virus would therefore appear to be in the nasal mucous membrane of mice of different age periods. In a later paper by Sabin and Olitsky,[26] observations of the above order have been confirmed and amplified. They conclude in part that " the resistance of old mice to peripheral inoculations of vesicular stomatitis virus appears to be the result of (a) changes produced by age not in the whole animal but in certain specific, isolated structures, and (b) the special mode of dissemination of peripherally injected virus." From this very brief review of work which has been accomplished on localized cell resistance it would appear that such a state may express itself when a variety of agencies are employed in an attempt to injure tissues.

The studies of an acquired fixed cell tissue resistance developing as a process of cell metaplasia secondary to tissue injury which have been discussed as emanating from this laboratory along with other observations of a confirmatory nature, would indicate that changes in the morphology of fixed tissue cells, with an assumed change in their chemical constitution, play a significant part in certain types of tissue resistance. The association of the age factor in the development of such a resistance is important, not only in prolonging through cell resistance the state of senescence but also in terms of the influence which fixed cells at different age periods may exert on the development of certain infectious diseases, both as a local tissue reaction and as more generalized invasions of the tissues of the host. Finally, this type of acquired resistance on the part of cells following injury may aid in filling in certain gaps in our understanding of tissue resistance as an acquired immunity which can not be satisfactorily explained either on a humoral (antibody) basis or in terms of the activity of wandering cells. These studies as a whole impress one with the lack of fixity on the part of cells which are supposed to be static and fixed, at least in their morphology. They suggest that change in configuration and, likely, in chemical constitution are essential characteristics of cell life and, furthermore, that such changes may not only be dependent upon injury and a tissue reaction of repair but may be due to the aging process expressing itself cytologically in organ life as well as in the organism as a whole.

BIBLIOGRAPHY

1. MacNider, W. deB.: The pathological changes which develop in the kidney as a result of occlusion by ligature of one branch of the renal artery, Jr. Med. Res., 1910, xv, 91–94.
2. MacNider, W. deB.: The pathological changes which develop in the kidney as a result of occlusion by ligature of one branch of the renal artery. Part II. Conclusion, Jr. Med. Res., 1911, xix, 425–454.
3. MacNider, W. deB.: A note on the regeneration of renal epithelium in the intact cat kidney, Jr. Med. Res., 1911, xx, 369–372.
4. Kaufman, E.: Lehrbuch der speziellen pathologischen Anatomie für Studierende und Arzte, Berlin, O. Reimer, 6 Aufl., Band, 1911, 815–818.
5. MacNider, W. deB.: A study of the renal epithelium in various types of acute experimental nephritis and of the relation which exists between the epithelial changes and the total output of urine, Jr. Med. Res., 1912, xxi, 79–126.
6. MacNider, W. deB.: The inhibition of the toxicity of uranium nitrate by sodium carbonate, and the protection of the kidney acutely nephropathic from uranium from the toxic action of an anesthetic by sodium carbonate, Jr. Exper. Med., 1916, xxiii, 171–187.
7. Chittenden, R. H., and Hutchinson, M. T.: Some experiments on the physiological action of uranium salts, Trans. Conn. Acad. Arts and Sci., 1888–1892, viii, 1.
8. Suzuki, T.: Morphologie der Nierensekretion, Jena, 1912.
9. MacNider, W. deB.: On the difference in the response of animals of different ages to a constant quantity of uranium nitrate, Proc. Soc. Exper. Biol. and Med., 1914, xi, 159–162.
10. MacNider, W. deB.: A consideration of the relative toxicity of uranium nitrate for animals of different ages, Jr. Exper. Med., 1917, xxvi, 1–17.
11. MacNider, W. deB.: The development of the chronic nephritis induced in the dog by uranium nitrate. A functional and pathological study with observations on the formation of urine by the altered kidneys, Jr. Exper. Med., 1929, xlix, 387–409.
12. MacNider, W. deB.: Urine formation during the acute and chronic nephritis induced by uranium nitrate, Harvey Society Lecture, Baltimore, 1928–1929.
13. MacNider, W. deB.: The functional and pathological response of the kidney in dogs subjected to a second subcutaneous injection of uranium nitrate, Jr. Exper. Med., 1929, xlix, 411–433.
14. MacNider, W. deB.: The development of an acquired resistance to bichloride of mercury by renal epithelium in the proximal convoluted tubule, Proc. Soc. Exper. Biol. and Med., 1937, xxxvii, 90–91.
15. MacNider, W. deB.: The liver injury induced by uranium nitrate. A consideration of the type of epithelial repair which imparts to the liver resistance against subsequent uranium intoxications, Jr. Pharm. and Exper. Therap., 1936, xlv, 359–372.
16. Whipple, G. H., and Sperry, J. A.: Chloroform poisoning, liver necrosis and repair, Bull. Johns Hopkins Hosp., 1909, xx, 278–289.
17. MacNider, W. deB.: The resistance of liver epithelium altered morphologically as the result of an injury from uranium followed by repair to the hepatotoxic action of chloroform, Jr. Pharm. and Exper. Therap., 1936, lvi, 373–381.
18. MacNider, W. deB.: The resistance to chloroform of a naturally acquired atypical type of liver epithelium occurring in senile dogs, Jr. Pharm. and Exper. Therap., 1936, lvi, 383–387.
19. MacNider, W. deB.: Concerning the persistence of an acquired type of atypical liver cell with observations on the resistance of such cells to the toxic action of chloroform, Jr. Pharm. and Exper. Therap., 1937, lix, 393–400.
20. Weller, C. V.: Tolerance in respect to the meningocerebral manifestations of acute and subacute lead poisoning, Arch. Int. Med., 1927, xxxix, 45.

21. SPRUNT, D. H.: Simple atrophy of the liver. Its relation to increased resistance, Arch. Path., 1937, xxiv, 738–742.
22. HUNTER, W. C.: Experimental study of the acquired resistance of the rabbit's renal epithelium to mercuric chloride, ANN. INT. MED., 1929, xi, 796–806.
23. SMYTH, H. F., SMYTH, H. F., JR., and CARPENTER, C. P.: The chronic toxicity of carbon tetrachloride; animal exposures and field studies, Jr. Indust. Hygiene and Toxicol., 1936, xviii, 277.
24. HAVILL, W. H., LICHTY, J. A., JR., and WHIPPLE, G. H.: III. Tolerance for mercury poisoning increased by frequent hemoglobin injections, Jr. Exper. Med., 1932, lv, 627.
25. OLITSKY, P. K., SABIN, A. B., and COX, H. R.: An acquired resistance of growing animals to certain neurotropic viruses in the absence of humoral antibodies or previous exposure to infection, Jr. Exper. Med., 1926, lxiv, 723.
26. SABIN, A. B., and OLITSKY, P. K.: Influence of host factors on neuroinvasiveness of vesicular stomatitis virus. III. Effect of age and pathway of infection on the character and localization of lesions in the central nervous system, Jr. Exper. Med., 1938, lxvii, 201.

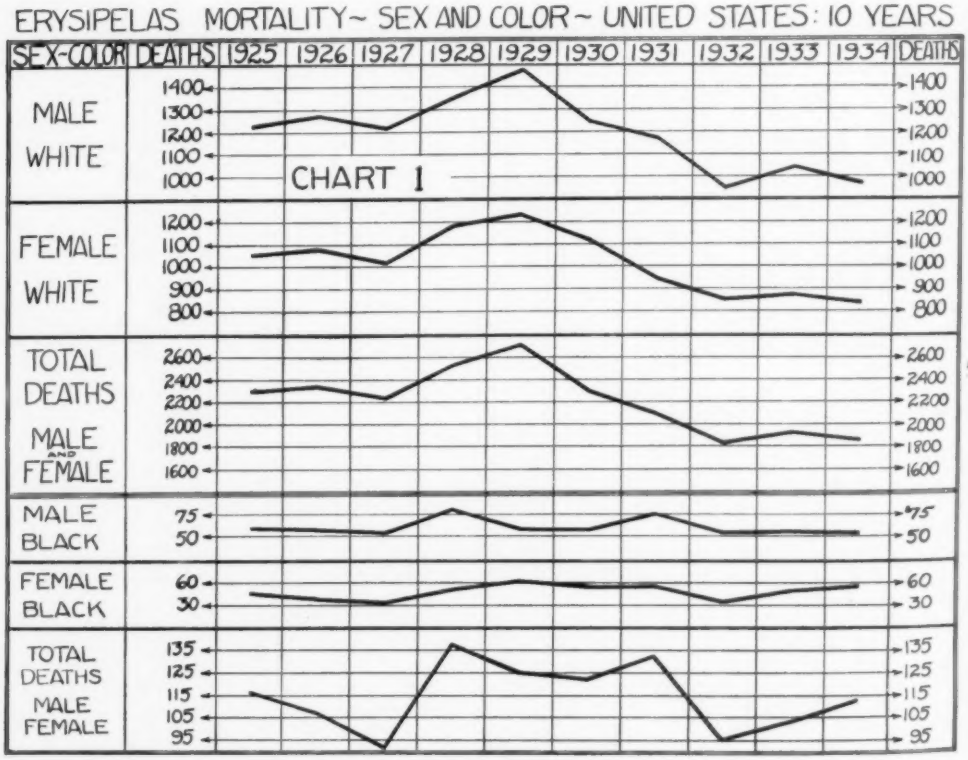
PROGNOSIS AND TREATMENT OF ERYSIPELAS *

By John A. Toomey, M.D., F.A.C.P., *Lakewood, Ohio*

Mortality statistics are the only sources of factual information not affected by the personal equation.

From 1912 to 1933, Hoyne in Chicago had a mortality rate of 12.47 per cent in 5,666 cases of erysipelas; from 1929 to 1933, it was 13.4 per cent in 1,193 cases. From 1927 to 1931, Gordon and Young [1] in Detroit had 1,156 cases with a mortality rate of 9.5 per cent. In Bellevue Hospital, in New York City, from 1904 to 1937, there were 15,277 cases with a mortality rate of 10.1 per cent.[2] Symmers [2] stated that in 3,311 cases admitted to the same institution in subsequent years and treated with antitoxin, the mortality rate was lowered to 7.1 per cent.

A curve of the total number of deaths from erysipelas in the registered areas of continental United States [3] for 10 years (1925 to 1934, inclusive) is shown in chart 1. Antitoxin was introduced in 1926. There was a

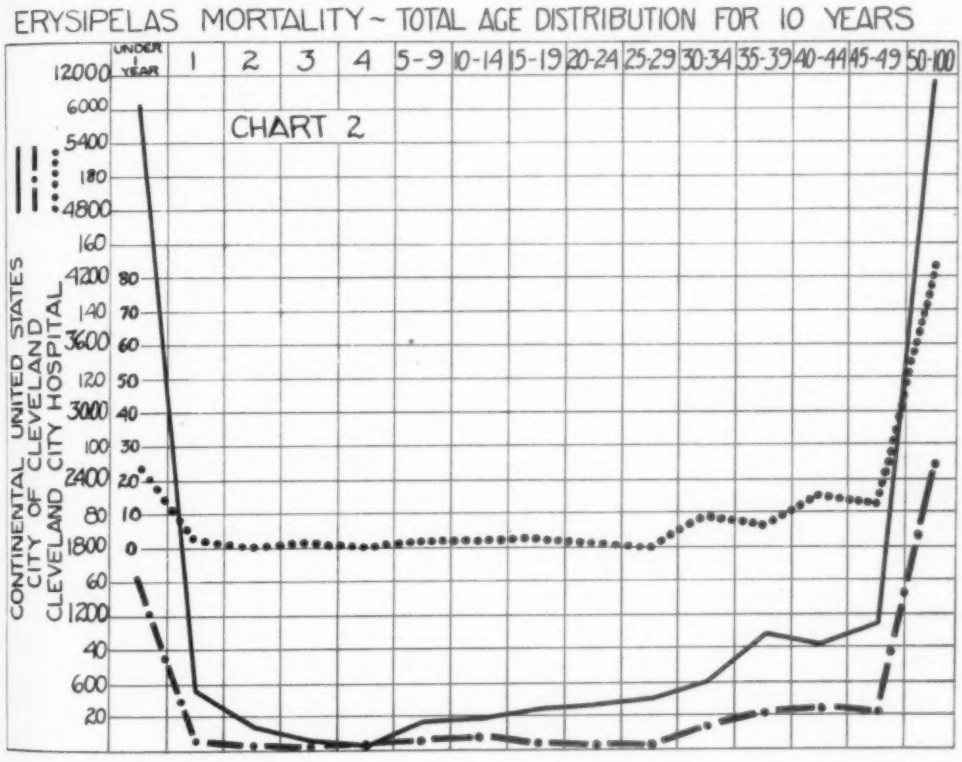


* Delivered before the American College of Physicians, New York City, April 6, 1938.

From the Department of Pediatrics, Western Reserve University, and the Division of Contagious Diseases, City Hospital, Cleveland, Ohio.

sharp rise in total mortality for the white race in 1928 and 1929 with a drop in 1930 and 1931, and a comparatively level period for the next two years. The mortality for the Negro race was $\frac{1}{20}$ that of the morbidity rate, although their population was nearly $\frac{1}{10}$ that of the white race. There was a rise in their total mortality in 1928 with a sustained high level in total cases to 1931, followed by a drop and a gradual rise again in 1933 and 1934.

It can be seen from chart 1 that less women die than men, both among the white and black races. The difference, although definite, is not extraordinary and might even be less apparent were the total morbidity known as well as the total mortality.



When statistics for the five years from 1925 to 1929 obtained from the Department of Commerce are examined, it is found that in the United States 3,654 deaths, or over 28 per cent of the total mortality from erysipelas during these years, occurred during the first year of life. Five thousand seven hundred and eighty-three deaths, or over 45 per cent of the total mortality, occurred in patients over 50 years of age. In short, 73 per cent of the total deaths occurred in the extremes of life. Between the ages of 10 and 50, there were 2,690 deaths, or 21 per cent of total deaths. It may be concluded that general mortality rates even without benefit of comparative morbidity rates confirm the impression that the mortality for adults between the ages of one and 50 years is comparatively low.

Conclusions cannot be drawn from statistics obtained from hospital case records unless the hospital's morbidity and mortality rates are compared with the total morbidity and mortality rates of the community in which the hospital is located. Such statistics were available for certain years; curves representing the total morbidity for 10 years (1925 to 1934, inclusive) have been drawn for the nation, the City of Cleveland, and Cleveland City Hospital (chart 2). The lines of the three curves tend to be roughly parallel.

In chart 2, attention should be called to the height of the lines representing deaths in infancy. Objection may be made, and rightly so, to the sharp rise in the curve as representative of the older age groups, i.e. from 50 to 100 years. The reason for this is because ages from 50 to 100 years were grouped together.

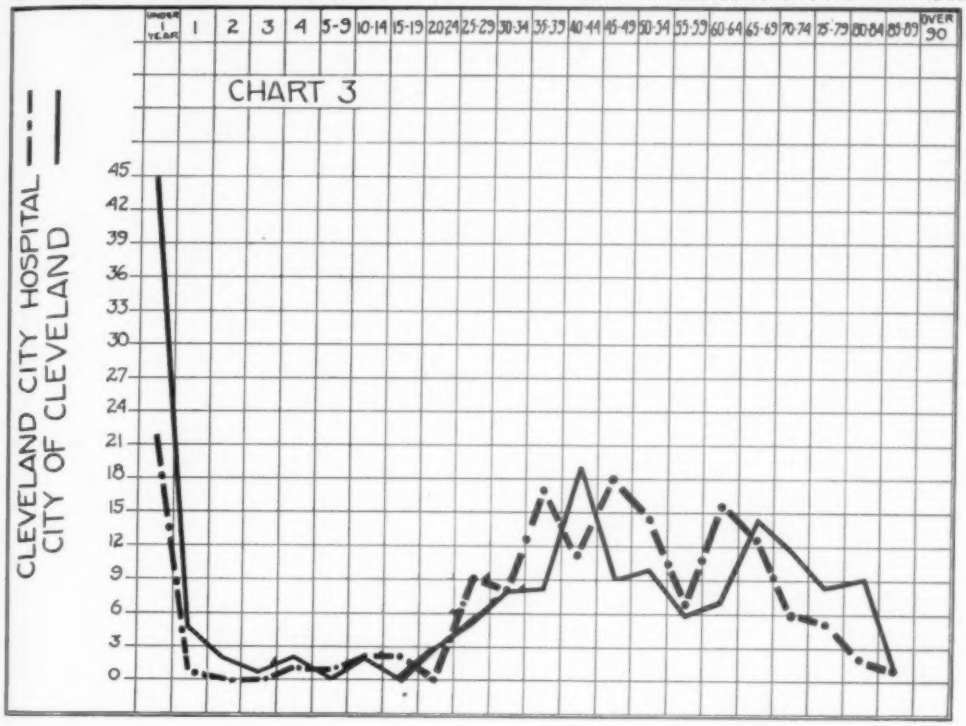
When the older age groups for the City of Cleveland and Cleveland City Hospital are split up as in chart 3, and the total deaths after the fifth year of life are grouped in five year periods, the curves for the later years rise, but are not so precipitous. Charts 2 and 3 show that age is a predisposing factor only in infancy. It is not clear that age in itself has anything to do with a total increase in deaths in later years. In fact, it is easy to show that it is not age itself, but conditions coincident with the aging process in human beings which predispose these individuals to a higher mortality.

These facts become even more obvious when a chart is made to show percentage mortality per 100,000 by age groups for Cleveland and Continental United States (chart 4).

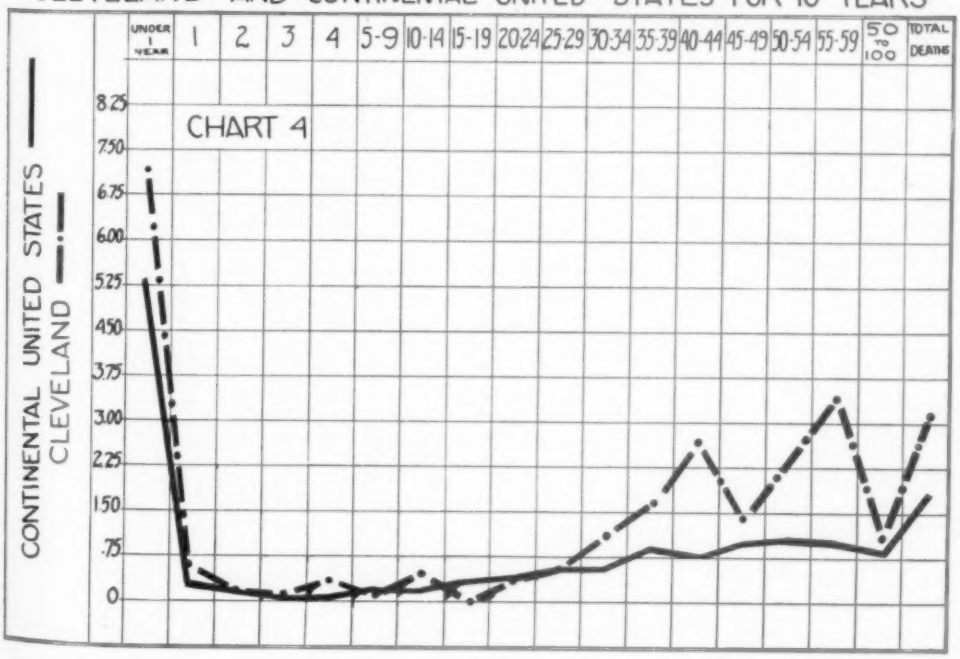
A most informative graph was drawn from data secured on the erysipelas mortality rate per 100,000 for Continental United States (chart 5). The figures quoted by Birkhaug [4] are used for the years 1906 to 1927, inclusive. Computations for the succeeding years 1928 to 1934 are made by using estimated population figures. Even allowing for gross errors, it will be noted that the total mortality rate per 100,000 has been falling even before the introduction of recent therapies—a greater fall before 1927 than afterwards. The figures for the yearly fall are not known, but roughly the curve would seem to have a gradual downward trend, reaching an even low in 1932.

General averages give erroneous impressions and inaccurate conclusions may be drawn when only the total death rates are examined. A curve of per cent mortality of age groups and total number of cases in each group for the City of Cleveland for the years 1925 to 1929, inclusive has been drawn in chart 6. The mortality rate for infants under one year was 49.4 per cent; between one and two years, 11.1 per cent; between two and three years, 6.6 per cent; between three and four years, 5.8 per cent, and between four and five years, 7.1 per cent. For the entire group from one to five years of age, it was 27.1 per cent. It can be seen that a sharp drop in percentage mortality occurs in the groups between 5 and 30 years of age, for although there were 236 cases, there were only eight deaths, a mortality

ERYSIPELAS MORTALITY BY AGE GROUPS: CLEVELAND 5 YEARS AND CLEVELAND CITY HOSPITAL 10 YEARS

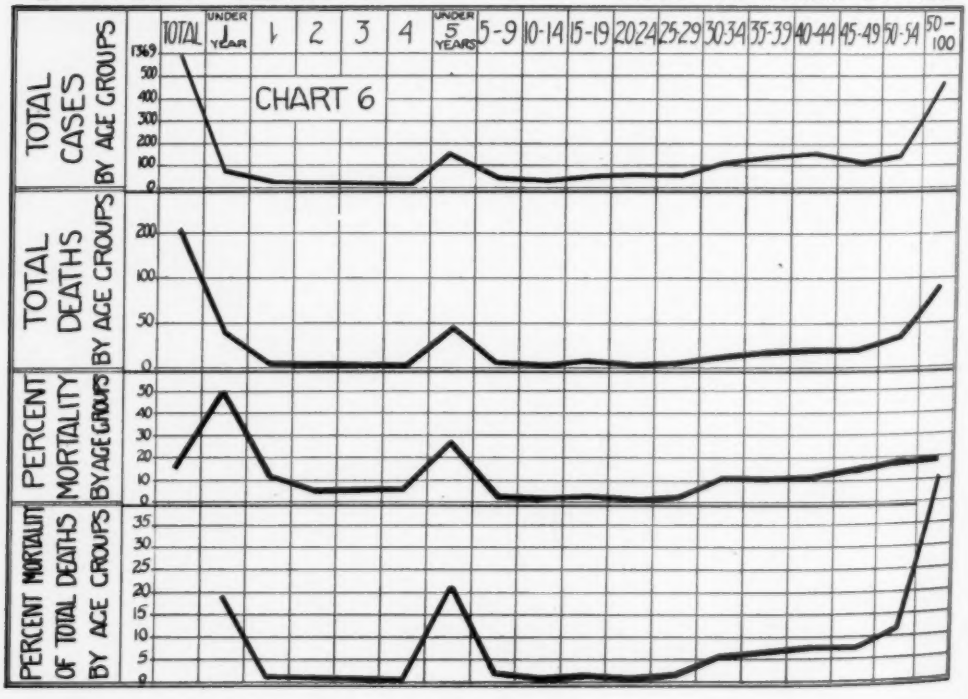


ERYSIPELAS: PERCENT MORTALITY PER 100,000 BY AGE GROUPS FOR CLEVELAND AND CONTINENTAL UNITED STATES FOR 10 YEARS



ERYSIPELAS: MORTALITY RATE PER 100,000 ~ CONTINENTAL UNITED STATES

ERYSIPELAS: CLEVELAND 1925-1929 --- CASES AND DEATHS BY AGE



rate of 3.3 per cent. Percentage mortality rises markedly for the older age groups. Few patients between the ages of 5 and 30 years die of erysipelas. It is evident that if the advantages for recovery that age seems to confer are ignored, and the treated cases are considered as a whole, statistics become meaningless. It might be stated as an axiom that as a rule a normal healthy young adult who contracts erysipelas always recovers.

Referring again to the statistics of Cleveland for the years 1925 to 1929, inclusive, it will be found that the mortality rate in infants under one year of age with reference to case incidence was 49.4 per cent, but the mortality rate of this group with reference to the total number of deaths was only 19.5 per cent. The case mortality rate of the age group, 5 to 49 years inclusive, was 9.7 per cent, but 31.4 per cent of the cases that died were in this group. The same is true of the old age group (from 50 to 100 years of age); the mortality rate was 19.8 per cent of the cases in that age group, although this represented 44.7 per cent of the total number of cases which died in this series.

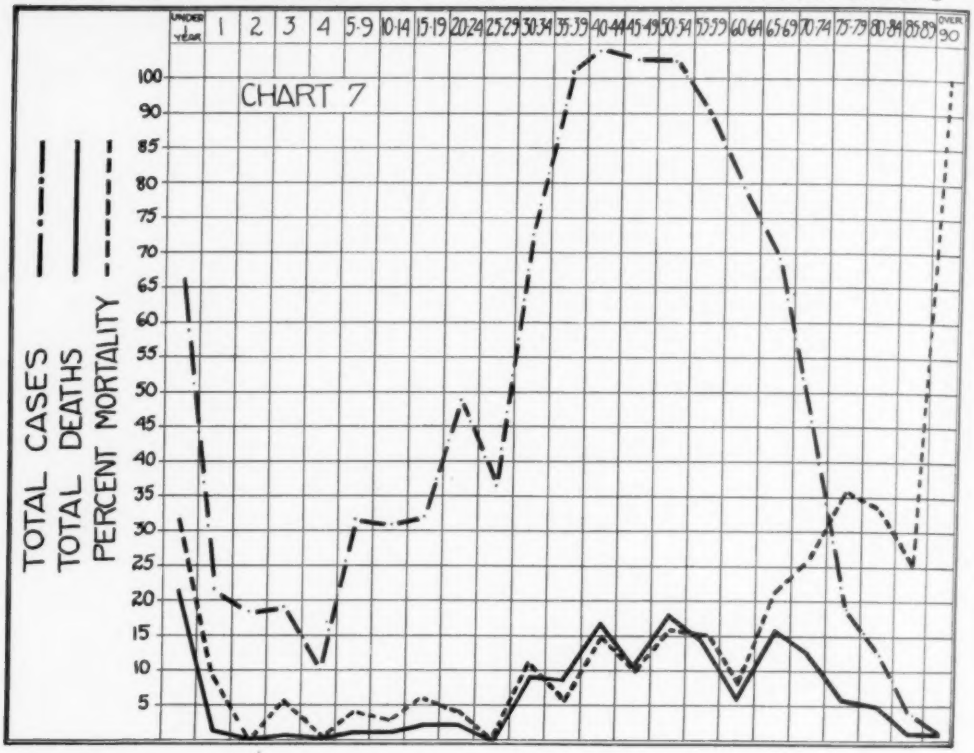
For the first five years of life, the number of deaths is approximately the same in both males and females of the black and white races. The fact that males in later life are more liable to contract erysipelas than females is probably due to increased chances of exposure and irritation. The average mortality rate in these years was 26.9 per cent for white males, 28 per cent for white females, 41 per cent for Negro males and 25 per cent for Negro females. The 41 per cent for Negro males is comparatively high, but this percentage difference was more apparent than real; it was not significant since the number of cases in this group was so few that a few cases one way or another would make a marked change in the percentage rate.

In chart 7, curves for the total deaths and cases, and the percentage mortality are drawn. It shows clearly the chances of survival in the various age groups.

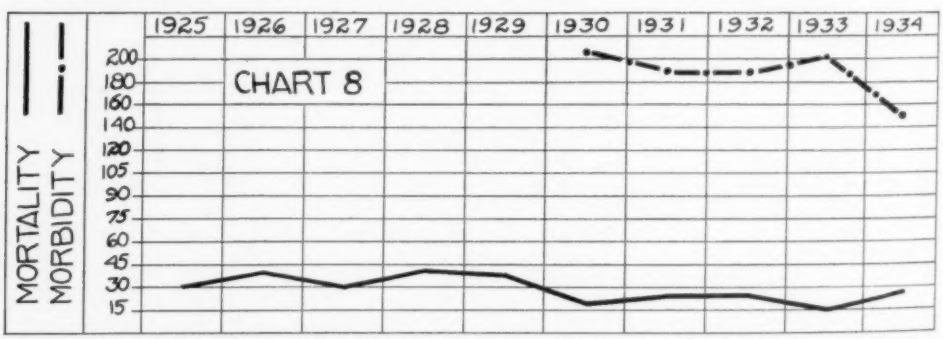
In chart 8, the morbidity curves for five years and the total mortality for 10 years for the City of Cleveland are drawn, while the morbidity and mortality rates are drawn for the Cleveland City Hospital for a 10 year period. The most important information gained from this chart is that the mortality of the hospital treated cases has remained about the same from 1932 to 1937, inclusive, although there was a drop in the total mortality for the hospital and the City of Cleveland in 1934. It showed also that the hospital has in some of the later years treated most of the cases that died in the community. The total number of deaths has dropped in the city since 1930, but the total number of hospital deaths has been rising since 1932. An increase in the hospital mortality rate means little if the total mortality rate of the community does not rise also.

Erysipelas may be the *coup de grace* that ends a long battle against some unrelated infection or degenerative organic condition, or merely an infectious episode experienced and recovered from long prior to the ultimate battle for existence. If to these possibilities are added the fact that the mortality and morbidity rates vary for different seasons of the year and

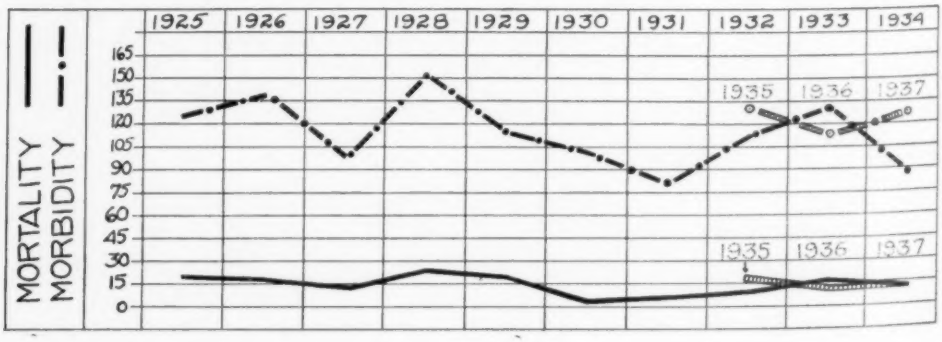
ERYSIPELAS: CLEVELAND CITY HOSPITAL ~ 1925-1934 BY AGE GROUPS



ERYSIPELAS MORTALITY AND MORBIDITY ~ CLEVELAND: 10 YEARS



ERYSIPELAS MORTALITY AND MORBIDITY ~ CLEVELAND CITY HOSPITAL: 13 YEARS



for different years as well, and that the erysipelas may be caused by organisms other than the streptococci (pneumococcus, *B. coli, B. typhosus,* staphylococci, etc.), then it can be seen how difficult it sometimes becomes to draw conclusions about therapeutic procedures from statistics.

Why do people die from this disease? When the records of the patients who died at Cleveland City Hospital during the period from 1925 to 1937, inclusive are studied, it is found that those who died were: (1) infants under one year of age, especially those with vulval or abdominal erysipelas (Group I); (2) patients over 50 years of age (Group II); (3) patients with pulmonary disease, such as tuberculosis, bronchopneumonia and lobar pneumonia (Group III); (4) patients with chronic organic disease, such as chronic myocarditis, valvulitis or arteriosclerotic disease (Group IV); (5) patients with concomitant acute infections such as influenza and other infectious or contagious diseases (Group V); (6) patients who had a severe debilitating illness immediately before the attack of erysipelas (Group VI); (7) patients with acute or chronic alcoholism (Group VII); (8) patients who had suffered some injury (Group VIII). Not all patients in these groups died, but all of the patients who died belonged to one of these groups. Only two patients died simply from erysipelas. They were both obese women with questionable pulmonary involvement. Those who were not in these categories recovered, regardless of how many attacks of erysipelas they had had, or how often the lesions had spread, or what kind of therapy was used. Thus, when good results are considered, those cases that fall outside the categories mentioned should be excluded.

GROUP I

Infants under One Year of Age
34 of 218 deaths (1925 to 1937, inclusive)
Cleveland City Hospital

Anemia, secondary	Otitis media, suppurative
Bronchopneumonia	Osteomyelitis
Cellulitis	Peritonitis
Fracture, skull	Prematurity
Malnutrition	Sepsis
Mastoiditis, bilateral	Septicemia
Meningitis	Syphilis, congenital
Nephritis, acute	Thrombosis, sinus

GROUP II

Patients over 50 Years of Age with Complications
80 of 218 deaths (1925 to 1937, inclusive)
Cleveland City Hospital

Abscess, lung	Emphysema	Nephritis, chronic
Abscesses, multiple	Furunculosis	Panophthalmitis
Aneurysm	Gangrene	Paralysis agitans
Arteriosclerosis generalized	Heart disease, passive congestive	Paresis, general
Arthritis	Hemorrhage, cerebral	Pericarditis, adhesive, chronic
Ascites	Hypertension	Psychosis, Korsakoff's
Asthma	Hypertrophy, prostate	Sclerosis, coronary
Bronchopneumonia	Infarct, lung	Septicemia
Carcinoma	Insufficiency, myocardial	Syphilis, tertiary
Cirrhosis, liver	Jaundice, toxic	Tuberculosis, kidney
Dementia, senile	Lymphangitis	Ulcer, duodenal
Diabetes	Myocarditis	Uremia
Edema, lungs	Nephritis, acute	Valvulitis, cardiac

GROUP III

Patients from 1 to 50 Years of Age (Mostly over 30 Years)
37 of 218 deaths (1925 to 1937, inclusive)

Cleveland City Hospital

Pulmonary Tuberculosis (4); Bronchopneumonia and Lobar Pneumonia (33)

GROUP IV

Patients from 1 to 50 Years of Age with Chronic Diseases
15 of 218 deaths (1925 to 1937, inclusive)

Cleveland City Hospital

Anemia, secondary
Diabetes
Elephantiasis
Heart disease, rheumatic (5)
Hepatitis, toxic
Nephritis, chronic
Pericarditis, adhesive and pleurisy, chronic with pneumothorax
Osteomyelitis
Silicosis
Stricture, urethral
Ulcer, peptic and vascular disease, diffuse

GROUP V

Individuals from 1 to 50 Years of Age with Other Acute Infections or Conditions
35 of 218 deaths (1925 to 1937, inclusive)

Cleveland City Hospital

Abscess, brain
Abscesses, multiple
Agranulocytosis
Arthritis, septic
Cellulitis
Cystitis
Dysentery
Empyema
Fistula, pulmonary, post traumatic
Gas bacillus infection
Glossitis, acute
Influenza
Lymphadenitis, suppurative
Mastoiditis
Meningitis
Osteomyelitis
Peritonitis
Pertussis
Pyelitis
Retention, acute urinary
Rubeola
Scarlet fever previous to erysipelas (3)
Septicemia
Serum sickness

GROUP VI

Cases up to 50 Years of Age with Previous Severe Infections
4 of 218 deaths (1925 to 1937, inclusive)

Cleveland City Hospital

Abscess, peritonsillar with streptococcus sore throat; influenza; pertussis; pneumonia.

GROUP VII

Adults up to 50 Years of Age with Delirium Tremens
6 of 218 deaths (1925 to 1937, inclusive)

Cleveland City Hospital

One case developed a psychosis, escaped from the hospital, returned and died as a result of exposure. He also had serum sickness.

GROUP VIII

Cases with Erysipelas Secondary to an Accident
4 of 218 deaths (1925 to 1937, inclusive)

Cleveland City Hospital

The types and kinds of complications are listed. Specific forms of treatment might be instituted because of the erysipelas in the infants (Group I) and in individuals with pulmonary and acute infections (Groups

III and V), and some decrease in mortality might be expected. A close study of the complications in other groups, however, makes us realize that they themselves may have created conditions very difficult to overcome. Most cases of erysipelas have a history of a previous acute or chronic upper respiratory infection immediately preceding the erysipelas, or a previous localized infection which has been irritated. The pneumonia which may develop often did not need the erysipelas to start it, being already present, and the erysipelas merely speeded up the exit.

Thus, in order to make a prognosis, one needs the information obtained from a history that has been carefully taken and a physical examination that has been meticulously performed.

Part II. Treatment

The value of any remedy for erysipelas should be gauged by its ability to save the patients who fall in those groups who usually die; the other patients get better anyway.

Prior to 1926, the treatment of this disease was anything but specific. Most endeavors were directed toward making the patient comfortable and watching for complications. In May 1926, Birkhaug [5] introduced erysipelas antitoxin. Various reports appeared. It was claimed that with the use of antitoxin the general appearance of the patient became better, the temperature and pulse rate dropped, the length of time the patient was ill was decreased, there were no extensions, the toxicity definitely diminished within from 12 to 18 hours after injections, there was a rapid disappearance or fading of the lesion and absorption of the pitting edema, and that the mortality rate was decreased. It is very difficult to evaluate statistics, but it should be easy to duplicate these experiences.

My report on therapy is only preliminary, but sufficiently complete to enable me to state that our patients have not responded in like manner. Cases of uncomplicated erysipelas that have merely a localized lesion without extensions are ill from about 2 to 14 days. The average is about seven days. The majority of our cases and the controls in our series that recovered began to show improvement between the fifth and eighth days. Unless some complications arise, it is unusual for the patient to be acutely ill longer than for this length of time. When spreads occur, it may take as long for the new lesion to clear up as did the original one. Many cases are not sick for even five or eight days.

In a study of 115 cases, McCann [6] concluded that antitoxin had no effect on the duration of fever and that the average stay in the hospital was not less in his serum treated group. He felt that a true objective examination for comparisons could only be made by studying the temperature charts.

Thus far, we have treated 520 cases between 1929 and 1938 with erysipelas antitoxin and have had 1,313 untreated control cases—755 from

1922 to 1929 and 558 from 1929 to 1938. Our cases have been treated with antitoxins purchased from various biological laboratories.

Serum sickness has occurred in a little more than 9 per cent of the cases. More than one dose of antitoxin was given to 239 patients as there was no clinical improvement after the intramuscular injection of one ampoule of antitoxin. Fifty-eight per cent of the total number of treated cases had extensions. The total mortality rate was 13 plus per cent. Thirty-five per cent of the untreated cases had extensions, and the mortality rate was 15.5 per cent. Infants seemed to derive some benefit from the use of antitoxin, as the mortality rate was decreased, confirming the results of Eley[7] and Blackfan.[8] In adults, however, the use of antitoxin did not lessen the number of hospital days. It did not cause an immediate decrease in the temperature curve or pulse rate, and in my experience, did not prevent the spread of the lesions of erysipelas.

The benefits that result from the use of newly discovered therapies are sometimes so obvious that control cases seem unnecessary. This is not true of erysipelas antitoxin. It was true, however, of diphtheria antitoxin when it was first introduced. From our experience with sulfanilamide in the treatment of erysipelas, it is believed that it is also true of this drug.

Approximately 50 cases were treated experimentally with antitoxin and various amounts of Prontylin * (sulfanilamide) before we finally came to treat erysipelas with this drug alone. All cases, save those with hepatitis, increasingly severe nephritis or sensitivity to sulfanilamide are now being treated in the following way. The dose for the first 24 hours is computed on the basis of 1 grain of sulfanilamide per pound body weight. One half of the total dose is given at once and the other half is given in divided doses over the first 24 hour period. Each succeeding day, until the drug is discontinued, the patient is given ½ grain per pound body weight. All but two patients have received this drug by mouth, and infants and patients in delirium are given it by stomach tube. Two patients were injected with the drug subcutaneously. When the drug was injected subcutaneously, 75 grains (5 grams) were added to 625 c.c. of saline, and the whole given as an infusion. All such doses are modifications of those suggested by Long and Bliss.[9] Rarely need this drug be given for more than four days unless there are local abscesses in addition to the erysipelas. Blood counts and hemoglobin estimations must be done daily and as soon as 400 grains have been given, the patient should be carefully reëxamined.

With antitoxin, the results were questionable save in the infant group. With sulfanilamide, they seem definite. Seventy-two of 76 cases thus treated with the latter have recovered and 3 have died, a mortality rate of 4 per cent. One of the cases that died was a 58 year old arteriosclerotic male who had been cured of erysipelas with sulfanilamide, had gone home against our advice and returned later with a recurrent attack, glomerular

* Furnished by the Winthrop Chemical Co.

nephritis and bronchopneumonia; another was a 70 year old male with arteriosclerotic heart disease and chronic pulmonary emphysema who died a few hours after admission; the third was a 35 year old male, with a gonococcal stricture of the urethra, a urethral fistula, extravasation of urine, cellulitis of the scrotum, pyelonephritis, hydronephrosis, uremia and syphilis, who died the day after admission. A 49 year old female with diffuse cellulitis of the leg, multiple abscesses, syphilis and toxic hepatitis was treated with one dose of sulfanilamide before the hepatitis was discovered. She died, but was not included in the treated series.

With the use of sulfanilamide, the lesions of erysipelas become dusky red and purplish within the first 12 to 24 hours and disappear completely within 4 to 10 days. The inflammatory reaction is likewise gone and the patient is subjectively better within 12 to 24 hours. No patient has had massive local desquamation following this treatment. The temperature comes down in a few days and usually by lysis. Only two of the cases had a spread of the lesion. However, there was only one spread in each instance and a very slight one.

If our experience is the general experience, sulfanilamide will become the drug of choice in the treatment of erysipelas. In cases of hepatitis or sensitivity to sulfanilamide, antitoxin may be tried on the basis that it can't do much harm and it might do some good.

An effort should be made to treat cases early, especially those cases in Groups I, III and V.

BIBLIOGRAPHY

1. Gordon, J. E., and Young, D. C.: Treatment of erysipelas with erysipelas streptococcus antitoxin, Jr. Michigan Med. Soc., 1929, xxviii, 353.
2. Symmers, D.: Antitoxin treatment of erysipelas; results in 705 cases at Bellevue Hospital, Jr. Am. Med. Assoc., 1928, xci, 535.
3. U. S. Department of Commerce, Mortality Statistics.
4. Birkhaug, K. E.: Erysipelas, Nelson's Loose Leaf Medicine, Chap. 16, pg. 447 et seq.
5. Birkhaug, K. E.: Erysipelas: Etiology and treatment with erysipelas antistreptococcic serum, Jr. Am. Med. Assoc., 1926, lxxxvi, 1411.
6. McCann, W. S.: Serum treatment of erysipelas, Jr. Am. Med. Assoc., 1928, xci, 78.
7. Eley, R. C.: Treatment of erysipelas in infants; report of 33 cases treated with antistreptococcus (erysipelas) serum, Am. Jr. Dis. Child., 1930, xxxix, 529.
8. Blackfan, K.: Personal communication to Birkhaug, K. E., 1928.
9. Long, H., and Bliss, E. A.: Para-amino-benzene-sulfonamide and its derivatives; experimental and clinical observations on their use in treatment of beta-hemolytic streptococcic infection; preliminary report, Jr. Am. Med. Assoc., 1937, cviii, 32.

THE PROBLEM OF THE DEVELOPMENT OF HYPERSENSITIVENESS IN MAN *

By FRANK A. SIMON, M.D., *Louisville, Kentucky*

FROM the standpoint of their development the several types of hypersensitiveness may be divided into two groups. Those in the first group are characterized by the fact that, in a given animal species, all individuals that are adequately exposed to a suitable allergen become sensitized. These types of hypersensitiveness, therefore, may be reproduced at will. In this group there are (*A*) the hypersensitiveness of infections, such as tuberculosis, pneumococcus infections, trichophyton infection, etc. (*B*) The hypersensitiveness which follows the parenteral injection of foreign substances, such as foreign blood serums (anaphylactic hypersensitiveness). (*C*) Contact eczema of the type which can be reproduced at will in laboratory animals or man.

In the second group the sensitivities are characterized by the fact that only a small percentage of exposed individuals become sensitized even though the exposure be very great and even repeated many times. They cannot be reproduced at will because the physiological conditions necessary for their establishment are unknown. They usually result from natural exposures —the allergen gaining entrance through the mucous membrane of the respiratory tract, the alimentary tract or through the skin. Occasionally, but not often, they follow parenteral injection; under these circumstances their occurrence is purely accidental, for previous injections of the same substance in the same individual and injections of the same substance in other individuals of the same species in many instances fail to sensitize. It is important to recognize that, in a given individual, repeated massive exposure may be entirely without effect whereas a subsequent exposure to the same substance, under external conditions which seem to be the same as before, may result in a very high degree of hypersensitiveness. Up to the present time these second types of hypersensitiveness have been observed only in man. This observation of their occurrence only in man may be the result of some peculiar human characteristic which is lacking in other animal species or, what is more probable, it may be due to our inadequate study of the other animal species. In this group there are (*A*) Atopic hypersensitiveness, which is characterized clinically by the conditions known as hay fever, asthma, atopic eczema, etc. (*B*) A condition closely related to atopic hypersensitiveness which occasionally follows the parenteral injection of such substances as insulin, pituitary extract, milk, horse serum, etc. (*C*) Contact eczema from such substances as nickel compounds, dyes, formalde-

* Received for publication August 7, 1937.
From the Department of Medicine, University of Louisville, School of Medicine.

hyde, ragweed pollen oil, etc., which cannot be produced consistently experimentally.

The classification of certain allergic conditions according to these criteria may seem to be somewhat difficult. For example, it is reported that monkeys and most human beings may be sensitized to poison ivy.[1, 2] Practically all normal guinea pigs may be sensitized to poison ivy.[3] Apparently this condition would be placed in group 1. The high degree of hypersensitiveness to poison ivy often seen clinically probably cannot be reproduced at will and hence (if this is true) would be placed in group 2. Most cases of hypersensitiveness to horse serum in man are relatively slight, can be reproduced at will and occur in all or nearly all injected individuals, hence they fall into group 1. The rarely observed, high degree of hypersensitiveness to horse serum in man, however, falls definitely into group 2. The type of hypersensitiveness found in serum sickness is placed definitely in group 1 even though serum sickness (the clinical expression of this hypersensitiveness) does not occur in a very large proportion of the cases. This is probably a special condition resulting from the injection of *large* amounts of serum.

Let us consider separately the development of these two groups of hypersensitiveness.

1. *Sensitivities Which May Be Induced with Regularity by Exposure to Allergens.* The hypersensitiveness which occurs in the infectious diseases (the increased sensitivity, increased response to the infectious agent) is apparently an expression of an immune process. The analogy between this response to the infectious agent in disease and the response to other parenterally introduced foreign proteins of non-infectious origin was called to our attention by Von Pirquet.[4] There is indeed a remarkable similarity between serum sickness and an infectious disease. In both cases there is a foreign agent introduced into the body from without, an incubation period, general malaise, aching pains in the joints, fever, a cutaneous eruption, convalescence and recovery. In the case of an infectious disease the infectious agent may produce, in addition to non-toxic antigens, substances which are primarily toxic; the agent may localize in and injure or destroy certain organs or tissues and in other ways complicate the picture, so that recovery does not always occur. The infectious agent lives and reproduces in the body and actively manufactures antigen in the body. In serum sickness the amount of antigen is limited to that which is introduced into the body from without.

There is also an analogy in the histological appearance of the lesions of certain infectious diseases and those produced in guinea pigs by the intradermal injection of second doses of human blood serum or turtle egg or even by the first injections of these substances at the time of the "flare."[5]

The influence of a tuberculous lesion in increasing the hypersensitiveness to such substances as horse serum and egg white also suggests a relationship

between infectious diseases and hypersensitiveness to foreign substances of non-infectious origin.[6]

In many pathogenic microörganisms exotoxins have not been found. The lesions and symptoms which result from infections with these organisms may be due, partially, to the ability of these organisms to live and reproduce in the body and manufacture non-toxic antigens to which the body becomes sensitized and which are thereby rendered injurious. These antigens may be primarily no more injurious than horse serum or egg white. Imagine, for example, an organism capable of living and reproducing and manufacturing horse serum in the human body and incapable of elaborating anything else. An infection with such an organism might result in a disease resembling serum sickness which might be more prolonged or more severe because of the continued supply of the antigen produced in the body.

The most plausible explanation for the existence of the hypersensitiveness which regularly follows the injection of foreign antigenic substances into the body of man or other animal species, is the similarity in chemical composition of these antigens and those of infectious microörganisms. The body is simply unable to distinguish between the antigens of infectious microörganisms and those of certain animals and plants which are not parasites. The differences which exist between hypersensitiveness of the anaphylactic type and that of infectious diseases in general and the differences which exist among various infectious diseases may be explained on the basis of differences in chemical composition, localization, or physical state of antigens, presence and nature of toxins, varying ability of the infectious agent to live and reproduce in the body, localization in, injury to, or destruction of essential organs with resulting alteration in physiology, etc.

2. *Sensitivities Which Have Not Been Induced with Regularity by Exposure to Allergens.* In passing to a consideration of the second types of hypersensitiveness described above, namely those types which cannot be induced at will, it is unfortunately necessary to continue to indulge in hypotheses. A consideration of these hypotheses together with some experimental evidence having a bearing upon them really constitute the chief purpose of this presentation. First we shall discuss atopic hypersensitiveness, by which we mean a type of increased reaction to a specific foreign substance characterized by the influence of an hereditary factor in its establishment, a characteristic local vascular response in a shock tissue known clinically as hay fever, asthma, atopic eczema, etc., and by the frequent but not invariable occurrence of a certain type of antibody in the blood known as atopic reagin. Other characteristics may be found in the following comparison, for which we are indebted to a great extent to Coca.[7]

Anaphylactic Hypersensitiveness and Atopic Hypersensitiveness Compared

Similarities. In both types there is a capacity to react with increased intensity to a specific foreign substance. This capacity is established by

previous contact with that substance (in atopic hypersensitiveness this latter statement is probable rather than certain).[7] The reaction is elicited by subsequent contact with the same substance. Antibodies are frequently present in the blood in both types. Skin tests may be obtained and shock induced by injections of the specific allergen.

Differences. Anaphylactic hypersensitiveness may be induced at will in various animal species including man by parenteral injection (or other contact) with certain foreign substances. Atopic hypersensitiveness cannot be thus induced but develops under certain natural conditions which have not been identified. It is definitely known, however, as a result of statistics and of overwhelming clinical evidence, that heredity plays an important rôle in its development. Atopic hypersensitiveness has been observed, thus far, only in man. The anaphylactic type of hypersensitiveness occurs in all, or nearly all, individuals exposed to suitable antigens while the atopic type occurs in only a small percentage of those exposed.

In any one animal species the symptoms and localization of the pathology of anaphylactic shock are qualitatively the same in all individuals of that species, i.e. the shock organ is constant. In atopic hypersensitiveness, on the other hand, this localization of symptoms and pathology (shock organ) is variable; thus we have localization in the nose, bronchioles, skin, etc. (hay fever, asthma, eczema, etc.).

Atopic hypersensitiveness (in man) is usually of much higher degree than anaphylactic hypersensitiveness in man.

There are important differences in the antibodies. Anaphylactic antibodies give precipitin and complement fixation reactions, are readily transferred to such laboratory animals as rabbits and guinea pigs but not readily transferred to the human skin locally, and are more resistant to heat. Atopic antibodies (reagins), on the other hand, do not give precipitin reactions, give only an unstable complement fixation with a large prezone, are not readily transferred to laboratory animals but may easily be transferred to the human skin locally, and are less resistant to heat.[7]

In consideration of these similarities and differences there are two possible attitudes which may be taken toward atopic hypersensitiveness. The first, emphasizing the differences, is that it is something radically different from the anaphylactic type, not related in any way at all, that the similarity suggested by name (hypersensitiveness, allergy) is an unfortunate mistake. The second view, emphasizing the similarities, is that the two conditions are essentially similar and closely related, the exact relationship, being unknown, need not be specified.

For the purpose of experimentation, I made the assumption that the two conditions are related in some way and planned experiments to throw light upon this relationship, should it exist.

Two possible relationships suggested themselves. First, that atopic hypersensitiveness represents an anomalous development of the anaphylactic form dependent upon certain conditions of exposure to allergens and upon

hereditary predisposition; that it represents perhaps an over-developed or an under-developed form of the anaphylactic type. This idea has been expressed by Rackemann as a "disturbance of the immune mechanism."[8] In order to investigate this hypothetical disturbance Rackemann, et al. compared the typhoid agglutinin response of asthmatic patients and normal persons. No significant difference, however, was found.[9] With the same object in mind, Simon and Rackemann studied the allergic response of atopic patients and normal persons to intradermal injections of guinea pig serum, and found no clearly defined differences.[10] In a further study of this problem, not previously reported, I gave repeated intradermal injections, to atopic patients, of the following substances: birch pollen, 1–50 dilution, 0.1 c.c. per injection; hen's egg white, 1–10 dilution, 0.1 c.c. per injection (and up to 0.5 c.c. undiluted egg white in 2 cases); cow's milk, undiluted, 0.1 c.c. per injection. There were twelve persons injected with each of the three substances named. The injections were given at weekly intervals for periods varying from six to ten weeks. In none of the 36 patients, however, was there evidence of the development of hypersensitiveness when skin tests were made by intradermal injection of the same substances. Hence we see that substances which are universally recognized as capable of producing a high degree of hypersensitiveness under natural conditions of exposure, when deliberately injected into atopic persons, did not produce hypersensitiveness. These findings are similar to those of Brunner.[18]

This failure to produce atopic hypersensitiveness by the injection of atopens is in agreement with the work of Walzer,[11] Cohen,[12] Sulzberger and Vaughan,[13] and others, who have conclusively demonstrated that, in normal persons and in atopic patients, following the introduction into the respiratory tract or into the gastrointestinal tract of such substances as fish, peanuts, ragweed pollen, silk, etc. the atopen circulates in the blood in a condition sufficiently unchanged so that it is able to preserve its specificity and produce an allergic reaction. This work indicates that the parenteral presence of atopens is of common occurrence and yet this presence of atopens does not, consistently, result in atopic hypersensitiveness, even in atopic patients. The theory that atopic hypersensitiveness is simply the result of the penetration of antigens through mucous membranes does not explain the facts and cannot be upheld.

As a possible explanation for the failure of development of atopic hypersensitiveness following the parenteral introduction of such atopens as hen's egg, cow's milk and birch pollen one might cite the work of Wells[14] on guinea pigs. In these experiments guinea pigs which had been fed egg were found to have become sensitized to egg and could be shocked by injections of egg. If, however, the feedings of egg were continued over a longer period the animals were found to have passed into a condition in which they could neither be shocked by injections of egg nor could they be further sensitized by injections of egg so that a subsequent injection would result in shock. The prolonged feeding seemed to have resulted in some such condition as

antianaphylaxis, resistance, or immunity. It might be argued that human beings do not become sensitized to hen's egg, cow's milk or birch pollen following injection of these substances because of previous continued contact with them.

In order to investigate this aspect of the problem I gave repeated intradermal injections to atopic patients of the following substances: mare's milk, undiluted, 0.1 c.c. per injection to 12 patients; turtle's egg, 1–10 dilution, 0.1 c.c. per injection to 12 persons. In none of the 24 persons was there evidence of the development of hypersensitiveness when skin tests were made by intradermal injection of the same substances. Mare's milk and turtle's egg are biologically similar respectively to cow's milk and hen's egg and in the case of turtle's egg the immunological specificity was investigated and found to be distinct from hen's egg, as shown by the following evidence: 3 guinea pigs sensitized to turtle's egg did not react to hen's egg, and two patients atopically sensitive to hen's egg, who gave large skin tests to hen's egg, gave no skin reaction at all to turtle's egg. Hence the idea of previous contact with the allergens of turtle's egg in the form of common allergens present in hen's egg cannot be upheld. This investigation, therefore, would indicate that the objection based on Wells' work is not valid, namely that previous continued contact with hen's egg does not constitute an explanation for the failure of development of atopic hypersensitiveness following parenteral injection of this allergen.

In contrast with this failure to produce atopic hypersensitiveness in man by injection of these allergens we have the ease with which the anaphylactic type may be produced in man by the injection of guinea pig serum.[9] This hypersensitiveness to guinea pig serum passes through the same stages as that observed in the guinea pig and undoubtedly represents the analogous phenomenon in man. A quantity of guinea pig serum less than 0.001 c.c. is sufficient to sensitize a man in some cases and 0.01 c.c. is sufficient in practically any case.

A second possible relationship between hypersensitiveness of the anaphylactic and atopic types is suggested by the work of Dienes with tuberculous guinea pigs in which it was shown that the injection of an antigen into a tuberculous lesion in a guinea pig results in the development of a much higher degree of hypersensitiveness than the injection of the same antigen into a normal animal. Since one of the characteristics of atopic hypersensitiveness is that it is often of much higher degree than anaphylactic hypersensitiveness in man, as measured by skin tests, one might suspect that atopic hypersensitiveness represents hypersensitiveness of the anaphylactic type which has been modified by infectious disease in an hereditarily predisposed individual. To be more specific one might form the hypothesis that a person with hereditary predisposition would develop ragweed pollen asthma provided he had an attack of acute bronchitis during the ragweed season, another such predisposed person would acquire grass hay fever because of an acute infectious rhinitis during the grass pollen season, and a third such per-

son might become sensitized to egg because egg happened to be the food taken in large amounts during an attack of enteritis.

In order to investigate this hypothesis patients with infectious diseases were exposed to two allergens. The allergens chosen were guinea pig serum and turtle egg, the former because it is a good antigen for man, the latter because it is a poor antigen for man, and both were selected because they are substances with which a later contact would be very unlikely. All patients were exposed to both substances in 1 to 10 dilution. The usual method of application was to apply to the nasal mucous membrane a cotton applicator saturated with the solutions, a method previously found to be effective in producing hypersensitiveness to guinea pig serum.[10] In addition many patients were given applications to the throat by swabbing with applicators saturated with the solutions. In several cases the solutions were also injected intradermally in quantities of 0.1 c.c. to each patient. In the entire series there were 18 patients. Of these, six had diphtheria, five measles, two scarlet fever, two streptococcic sore throat, one mumps, and two chicken pox. Approximately three weeks after treatment with turtle egg and guinea pig serum skin tests were made in all cases by intradermal injection of these substances in dilutions of 1–10 and 1–100. The results were the same in all cases, that is, all gave positive skin tests to guinea pig serum and all negative tests to turtle egg. All patients reacted to these allergens just as one might expect them to react had they not been sick with an infectious disease, with the exception that in a few cases the hypersensitiveness appeared to be somewhat weaker than one might expect in a healthy subject. As controls there were a series of more than 100 persons sensitized to guinea pig serum (by intradermal injection and by application of the serum to the nasal mucous membrane) and the twelve patients previously discussed who were injected with turtle egg.

Apparently the infectious disease was without influence on the development of the hypersensitiveness except perhaps to weaken it in several cases. There was no evidence of an increased sensitivity greater than in the controls in any case. The allergen was introduced as early as possible in the course of the disease but in every instance the disease was clinically well developed when the exposure was made. This may constitute an objection and explain the negative results, since, according to the experience of Dienes, the antigen must be injected into the tuberculous lesion early in the course of the infection. Since the patients were chosen at random rather than selected on the basis of atopic history, the presence of an hereditary predisposition in any is not guaranteed. From the evidence available, however, it is apparent that the infectious diseases studied did not increase the degree of hypersensitiveness and certainly did not make it possible to produce atopic hypersensitiveness at will by exposure to allergens.

It must be concluded, therefore, that these experiments planned to investigate a possible relationship between the atopic and the anaphylactic types of hypersensitiveness have failed to disclose such a relationship.

The hypersensitiveness which occasionally occurs following the injection of such substances as insulin,[15] pituitary extracts,[16] liver extract,[20] etc. is sometimes of very high degree, may be accompanied by the presence of antibodies of the atopic type (reagins) and occurs in only a small percentage of exposed persons. The presence of an hereditary influence in its establishment is probable. Hence it resembles atopic hypersensitiveness. It often differs, however, in one important respect, namely in the absence of a typical atopic clinical syndrome such as hay fever, asthma or atopic eczema. This absence of an atopic syndrome may be due to the fact that exposure to biological products such as insulin and pituitary extracts is usually by parenteral injection rather than by inhalation or ingestion. This type of hypersensitiveness resembles the atopic type more closely than any other recognized variety and may fundamentally be identical with the atopic type, modified in its manifestations and in its mode of establishment only by the route of exposure to the allergen. The fundamental importance of the predisposed shock organ in atopy should constantly be held in mind, however, and with the evidence at present available a definite decision is not justified on this point.

Concerning hypersensitiveness to drugs of several clinical forms such as a number of clinical varieties of skin eruptions, asthma, purpura, etc., the evidence suggests that the true allergen is a combination of the drug with body proteins. Hence, with the exception of the origin of the allergen, there is no fundamental reason for regarding this type of hypersensitiveness as differing from those due to the usual inhalants and foods. It may be atopic in some cases and non-atopic in others.

In the hypersensitiveness seen in contact eczema the epidermis plays an important part. The reactions are always of a delayed type for the obvious reason that vascular changes cannot occur in the epidermis, since it is not a vascular tissue. Concerning the establishment of this type of hypersensitiveness we know very little. Heredity is not known to be a factor, but this aspect of the problem has not been carefully studied. With most of the allergens of contact eczema, such as nickel salts, quinine, azo dyes, mercury compounds, formaldehyde, etc. only a small percentage of exposed persons become sensitized.

In the case of poison ivy, however, Straus reports that it is possible to sensitize a majority of human infants and monkeys.[1, 2] Practically all normal guinea pigs may be sensitized to poison ivy.[3] Spain reports that about two-thirds of apparently normal human adults are sensitive to poison ivy in varying degree, the percentage reacting to any given concentration of poison ivy extract being proportional to the logarithm of the concentration of the test extract.[17]

In consideration of these data it appears reasonable to assume that there are two types of contact eczema, analogous respectively, from the developmental standpoint, to atopic and anaphylactic hypersensitiveness. The type usually seen clinically is analogous developmentally to atopy and cannot be

reproduced at will experimentally. The type which can be produced at will in guinea pigs, monkeys or in human infants by exposure to poison ivy is analogous to anaphylactic hypersensitiveness. This latter type, in the guinea pig and monkey (and probably also in artificially sensitized human infants) is very much weaker than the usual clinical case of ivy poisoning. It is also well to remember, in dealing with a substance such as poison ivy, that primary irritation may be confused with allergic reaction. Poison ivy extract is definitely irritating to the skin of a guinea pig even before sensitization has developed. Hence it is worth inquiring, in the case of the work reported by Spain, referred to above,[17] whether those persons who reacted to the very strong extracts did so as a result of allergic sensitivity or as a result of the primary irritation of the extract used in the test.

To illustrate this concept more specifically, poison ivy sensitivity produced experimentally in human beings, monkeys and guinea pigs is analogous (developmentally) to horse serum sensitivity produced experimentally in human beings and in guinea pigs, whereas clinical ivy sensitivity in man is analogous to the rarely encountered, high degree of sensitivity to horse serum in man. It is true that *occasionally* a very high degree of sensitivity to horse serum and to poison ivy may be produced "experimentally."[19] The significant fact is that neither can be *consistently* produced experimentally. (My technician and I have repeatedly spilled strong poison ivy extracts on our hands without having become sensitized, and I have deliberately tried to sensitize myself without success.)

In considering once more the general problem of the development of hypersensitiveness in the second group of sensitivities, namely those which cannot be produced consistently experimentally, the present need is not to attempt to decide what relationship, if any, exists between these two groups but rather to study the sensitivities themselves more thoroughly in order that we may learn the facts which will enable us to decide what relationship, if any, exists between them.

In studying these sensitivities which cannot be produced experimentally there are several important and fundamental problems to be investigated. Among the more important of these there are two which would seem to deserve special consideration. First, what factors determine that some individuals become sensitized whereas others in the same environment with apparently the same exposures are exempt? Second, among those who become sensitized what determines the specific substances to which hypersensitiveness develops? With regard to the first problem we need to investigate the physiological conditions under which it is possible for these types of hypersensitiveness to develop. The influence of heredity in atopy should be investigated further and should be regarded as a challenge to determine its physiologic mode of action. The influence of heredity does not remove this problem from physiologic investigation. The influence of heredity in the etiology of diabetes mellitus, for example, is generally recognized and yet the study of diabetes from a physiologic standpoint has been of great

practical value in the understanding and treatment of the disease. The possibility of other factors in addition to exposure to atopens and heredity must also be investigated. The clinical evidence suggests that, in the case of atopy, patients are in a condition predisposed to the development of hypersensitiveness for relatively brief intervals rather than continuously throughout their lives or continuously after a certain period of their lives. In support of this concept we have the following evidence: 1. Injection of such substances as pollen extracts, insulin, pituitary extracts, liver extract, horse serum, guinea pig serum, etc. into atopic patients very rarely if ever results in the production of atopic hypersensitiveness. 2. In the rare instances in which the injection of such substances results in a high degree of hypersensitiveness with reagins (the atopic nature of which has been questioned, chiefly on the basis of the absence of an atopic syndrome) previous injections of the same substance and subsequent injections of other atopens frequently are without effect in producing hypersensitiveness. 3. Many persons living in the ragweed pollen area have inhaled this pollen every fall for many years without having become sensitized to it, while during this same period of their lives they have become sensitized to other pollens present in the air at some other season, such as timothy, oak, birch, etc.

The second problem to which reference was made, namely the determination of the specific allergens to which sensitization develops, may be closely related to this first problem. Two possibilities suggest themselves. (1) That the capacity to become sensitized is specifically directed toward some particular substance and not toward other substances.[7] According to this interesting theory one man becomes sensitized to ragweed pollen because he has been born with the inherited capacity to become sensitized to this substance and he does not become sensitized to grass pollens because of the absence of the hereditary determiners for sensitization to grass pollens (or absence of exposure to grass pollens). (2) Another, and perhaps more plausible hypothesis, would be one which supposes a nonspecific predisposition to the development of hypersensitiveness, present for comparatively short intervals of time, the specific allergen to which hypersensitiveness develops being determined by the following circumstances: (*A*) Exposure to that particular allergen, (*B*) the coincidence of this exposure with the period of predisposition, (*C*) some accidental occurrence at the time of exposure (such as an infectious disease, evidence for which was not found in the experiments described above). In support of this hypothesis one may cite the following clinical evidence, which is in the nature of a clinical impression rather than statistical evidence: (1) Patients sensitive to wheat are usually sensitive to several of the separate protein constituents of wheat rather than to only one of these constituents. This would indicate that the simultaneous exposure to several substances, all of which are good allergens, results in hypersensitiveness to each of the several substances. This concept is also in agreement with the well recognized fact that allergic patients are usually sensitive to more than one substance. (2) Patients sensitive to tree

pollens are often sensitive to two or more tree pollens which are in the air at the same time interval even though these trees are of unrelated species and probably do not contain common allergens. A study of sensitivity to the individual components of mixtures of allergens and a statistical study of sensitivity to pollens in the air at the same time would be of value in contributing to the solution of this problem.

REFERENCES

1. Straus, H. W.: Artificial sensitization of infants to poison ivy, Jr. Allergy, 1931, ii, 137.
2. Straus, H. W.: Studies in experimental hypersensitiveness in the rhesus monkey, 1. Active sensitization with poison ivy, Jr. Immunol., 1937, xxxii, 241.
3. Simon, F. A., Simon, M. G., Rackemann, F. M., and Dienes, L.: The sensitization of guinea pigs to poison ivy, Jr. Immunol., 1934, xxvii, 113.
4. Von Pirquet, C., and Schick, B.: Zur Theorie der Incubationzeit; Vorlaufige Mitteilung, Wien. klin. Wchnschr., 1903, xvi, 758.
5. Dienes, L., and Simon, F. A.: The flaring up of injection sites in allergic guinea pigs, Jr. Immunol., 1935, xxviii, 321.
6. Dienes, L., and Schoenheit, E. W.: The reproduction of tuberculin hypersensitiveness in guinea pigs with various protein substances, Am. Rev. Tuberc., 1929, xx, 92.
7. Coca, A. F., Walzer, M., and Thommen, A. A.: Asthma and hay fever in theory and practice, Chas. C. Thomas, pgs. 38 to 57.
8. Rackemann, F. M.: The nature of allergy, Trans. Am. Clin. and Climat. Assoc., 1930, xlvi, 72.
9. Rackemann, F. M., Simon, F. A., Simon, M. G., and Scully, M. A.: Further observations on the nature of allergy, Jr. Allergy, 1933, iv, 498.
10. Simon, F. A., and Rackemann, F. M.: The development of hypersensitiveness in man, Jr. Allergy, 1934, v, 439.
11. Walzer, M.: A direct method of demonstrating the absorption of incompletely digested proteins in normal human beings, Jr. Immunol., 1926, xi, 249.
12. Cohen, M. B., Ecker, E. E., and Rudolph, J. A.: Disappearance time of circulating ragweed pollen material after absorption from nose and throat, Jr. Allergy, 1930, i, 529.
13. Sulzberger, M. B., and Vaughan, W. T.: Experiments in silk sensitivity and the inhalation of allergen in atopic dermatitis, Jr. Allergy, 1934, v, 554.
14. Wells, H. G.: The present status of the problems of anaphylaxis, Phys. Rev., 1921, i, 44.
15. Tuft, L.: Insulin hypersensitiveness, immunologic considerations and case reports, Am. Jr. Med. Sci., 1928, clxxvi, 707.
16. Simon, F. A., and Ryder, C. F.: Hypersensitiveness to pituitary extracts, Jr. Am. Med. Assoc., 1936, cvi, 512.
17. Spain, W. C., Newell, J. M., and Meeker, M. G.: The percentage of persons susceptible to poison ivy and poison oak, Jr. Allergy, 1934, v, 571.
18. Brunner, M.: Active sensitization in human beings, Jr. Allergy, 1932, iii, 521.
19. Field, H., and Sulzberger, M. B.: Experiments in poison ivy sensitivity, Jr. Allergy, 1936, vii, 139.
20. Criep, L. H.: Personal communication.

ELECTROPYREXIA; TECHNIC OF APPLICATION AND THERAPEUTIC INDICATIONS *

By STAFFORD L. OSBORNE, B.P.E., and D. E. MARKSON, M.D., F.A.C.P.,
Chicago, Illinois

THE technic of artificial fever has changed considerably during the last three years. The field of usefulness of artificially induced fever has widened considerably and in spite of over-enthusiasm of some, and the tendency to use it without any regard to cause and effect by others, it is now recognized to be quite useful in the field of therapeutics. Paralleling this increase in usefulness, several different kinds of apparatus for producing fever have been developed, the use of which has led to much confusion.

The first problem that arises when one desires to employ artificial fever as a therapeutic procedure is: What method should be used? From the literature, this question is not readily answered for several reasons. One reason is, that it is not difficult to convince oneself that the apparatus one is using and accustomed to is the ideal, and that any deviation from such an apparatus and method is radically wrong. The second reason is, that a well-trained personnel is of vital importance in administering artificial fever, and that such a personnel can use successfully any of the well-recognized methods. Yet it is believed that such a group should not labor under a handicap if real differences exist; therefore, a careful consideration of the method to be employed is in order.

At present there are two distinct methods used for producing artificial fever in man. *First,* by means of an externally heated environment. Examples are the air-conditioned Kettering hypertherm, infra-red radiation, such as the electric light cabinets, and hot water baths. *Second,* the production of heat in the body by means of high frequency currents such as diathermy, high frequency electric fields, or electromagnetic induction.

The use of hot water is too dangerous a procedure to be given any consideration. Mehrtens and Poupourit [1] who introduced the hot water bath method were unable to maintain the temperature of their patients for more than a few hours. That temperature can be maintained by this method was first demonstrated by Merriman and Osborne.[2] These authors state, however, that this is the most dangerous method so far devised, and advise against its use.

We first employed the high frequency current as introduced by Neymann and Osborne.[3] Since then we have tried every method advocated up to the present time in an endeavor to find the best method available. Our experiences have led us to the conclusion that the use of high frequency current

* Received for publication July 22, 1937.
From the Department of Physical Therapy and the Department of Medicine, Northwestern University Medical School, Chicago, Illinois.

for producing artificial fever has a much wider margin of safety for the patient than external heating methods, and is far more comfortable. These observations were largely empiric in nature at first but gradually physiological investigations are tending to substantiate the bedside observations. Neymann and Osborne [4] have shown that when external heat was used the natural heat gradient of the body was reversed, while this was not true when high frequency currents were used to produce internal heating. (Figure 1.) They also showed that there is a greater water loss by way of the skin (table 1), when internal heat is used.

TABLE I

Effect of External and Internal Heat on Perspiration Output. Less Danger of Heat Stroke When the Patient Is Perspiring Freely *

Patient Number	Type of Treatment	Date	Temperature Above 103.5° F.	Temperature Above 105.8° F.	Water Intake	Calculated Perspiration Output
1	Blanket	Mar. 16	8 hr.	4 hr.	2,290 c.c.	4,340 gm.
1	Diathermia	Apr. 3	8 hr.	4 hr.	2,575 c.c.	5,048 gm.
2	Blanket	Mar. 23	8 hr.	4 hr.	2,350 c.c.	3,491 gm.
2	Diathermia	Apr. 3	8 hr.	3½ hr.	3,375 c.c.	4,683 gm.
2	Radiothermia	Apr. 6	10¼ hr.	4 hr.	3,420 c.c.	4,216 gm.
3	Blanket	Nov. 28	8 hr.	2¼ hr.	3,250 c.c.	3,453 gm.
3	Diathermia	Dec. 8	8 hr.	2¼ hr.	5,200 c.c.	6,141 gm.
3	Radiothermia	Dec. 18	7¾ hr.	2½ hr.	4,110 c.c.	3,960 gm.

* NEYMANN, C. A , and OSBORNE, S. L.: Am. Jr. Syph., January, 1934.

Gibson, Kopp and Evans [5] reported at the International Fever Conference, 1937, their studies in plasma volume. They stated that with the Kettering hypertherm air-conditioned cabinet, reduction in blood volume was extreme, and occurred early in the course of fever reduction, with the result that a severe degree of tissue dehydration takes place by the time therapeutically desired temperatures were obtained. With diathermy, a considerable reduction in plasma volume did not take place until high temperatures had been reached. These investigators state that, in their opinion, the degree of dehydration and danger of serious circulatory disturbance is considerable during fever induced by the Kettering hypertherm, even when fluids are liberally given by mouth. Our observations have confirmed their opinion. Gibson, Kopp and Evans also showed that the degree of alkalosis was most marked in patients treated by externally applied heat. Moreover, we have found that the pulse rate was usually lower by approximately 20 beats per minute when internal heat was used as opposed to the findings with external heat (figure 2). Again, the high environmental temperature to which the patient is exposed throughout the treatment when external heat is

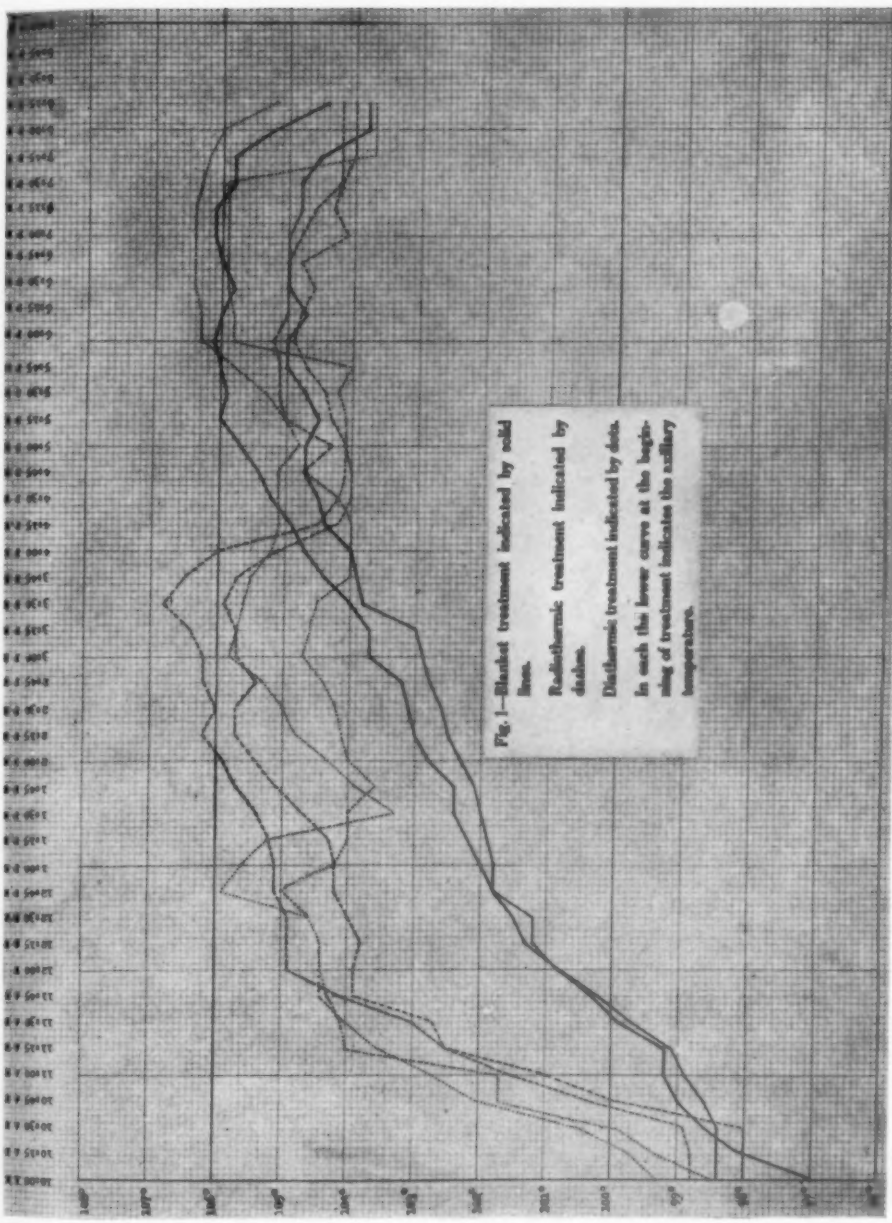


FIG. 1. Comparison of external and internal heating of the body. External heat reverses the natural heat gradient. (Neymann and Osborne, Physiology of hyperpyrexia, Am. Jr. Syphilis and Neurology.)

used, apparently predisposes more readily to heat stroke and circulatory collapse. Delirium seems to be more frequent.

Regardless of the method used, it is imperative that careful attention be given to prevent heat loss from the patient if a temperature is to be maintained for a number of hours. Successful temperature maintenance depends on this.

In this respect marked progress has been made. The methods first advocated seem very crude today. The use of a treatment bag (which is

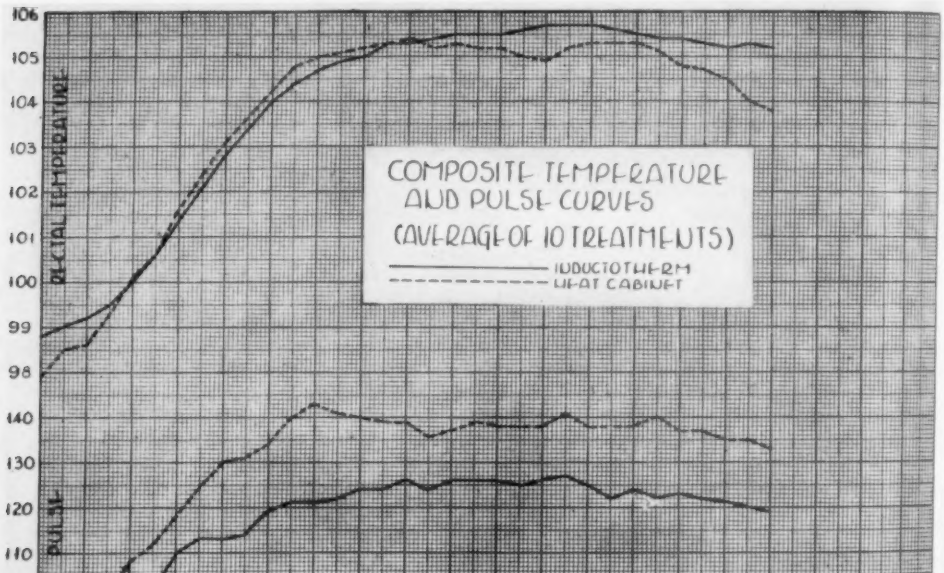


FIG. 2. Effect of external and internal heat on pulse rate.

essentially a well-insulated sleeping blanket) was a distinct step forward, but this has certain disadvantages, such as the restriction of the patient's movements and the weight of the bag upon the patient, particularly upon the feet. It is not easy to keep the bag clean. These disadvantages have been successfully eliminated by the use of some form of cabinet to retard heat loss and at the same time use the high frequency current to raise the body temperature to the desired therapeutic level. A wooden cabinet with air conditioned features has been used, but such a cabinet has the disadvantage of warping and of being quite heavy and bulky. Nevertheless it was a step in the right direction. Recently a much cheaper and more durable cabinet

has been devised. It is so light and portable that it may be moved to any room in the hospital, and is constructed almost entirely of polished metal (figures 3, 4, 5). We believe that such a cabinet will largely supersede the "zipper treatment bag."

We shall first describe the "zipper bag treatment technic." Our method is as follows: The bag is fully opened and one-half of the bag placed on the bed so that when the patient lies down, the middle of the neck is level with the top of the bag. A full-sized rubber sheet is laid over this to prevent heat loss through the bag and to keep the bag as dry and clean as possible. Next, a bath blanket, or a light woolen blanket folded like a shawl, is placed over the rubber sheet at the upper end with the apex of the shawl directed toward the foot of the bed. This blanket serves the purpose of preventing heat loss from the region of the neck when the zipper bag is closed. *Next,* a special terry cloth is laid over the entire rubber sheet and shawl-shaped blanket. The cloth must be so placed that the open side, when the cloth is folded over to cover the patient, will be towards the special opening provided in the bag to obtain access to the patient once the bag is closed. After the patient is covered with the terry cloth, it is quite closely approximated around the neck and shoulder, and held in place with a safety-pin. *Next,* the shawl-shaped blanket is brought around and fitted snugly to the neck to prevent the escape of heat from the bag. The zipper bag is now closed and the 12-foot cable, to be connected later with the electromagnetic generator, is formed into a single eliptical loop about four feet long and one foot wide. It extends approximately from the shoulder level to the middle of the lower leg (figure 6). Occasionally it is necessary to fold the blanket into two thicknesses and place it under the coil in the region of the lower legs, if the patient complains of too much heat in that region. A full length rubber sheet is placed over the coil and two additional blankets are added when necessary. The coil is now connected to the inductotherm and the current turned on.

The *electromagnetic cabinet technic* is very simple. The cabinet is opened (figure 4) and a large terry cloth is folded and so placed over the special mattress that the patient will lie on the lower half and be covered with the upper half. The cabinet is then closed, the neck outlet is closed with a pillow, and the heater and humidifying apparatus is turned on to preheat the cabinet to 110° F. This is to prevent the transfer of heat from the patient whose temperature is approximately 98.6° F. to the air of the cabinet. When 110° F. is reached, the patient is placed between the layers of terry cloth (care being taken to well insulate around the neck), the cabinet closed and the electromagnetic generator turned on (figure 5). When the patient's rectal temperature reaches the desired level, the electromagnetic current is turned off and the required temperature level is maintained by regulation of the cabinet temperature which is accomplished by a variable resistance switch. The ideal cabinet temperature is the lowest that will retain the patient's temperature level. This cabinet temperature should not exceed 110° F. and is usually kept between 100° to 105° F. A special opening is provided for taking care of the patient's needs, such as the bed pan, and for rectal temperature readings or other necessary observations. The heated air is circulated and humidified to between 90 and 95 per cent, although humidification is not automatically controlled.

Before prescribing fever, the physician should determine whether it is of therapeutic value for the disease under consideration. Lack of confidence on his part is usually unconsciously transferred to the patient. The treatment produces discomfort and does so because the patient is hot and his body temperature above its normal range. The degree of discomfort varies with the patient and the method used to raise the temperature. Patients should be prepared for the discomfort, but

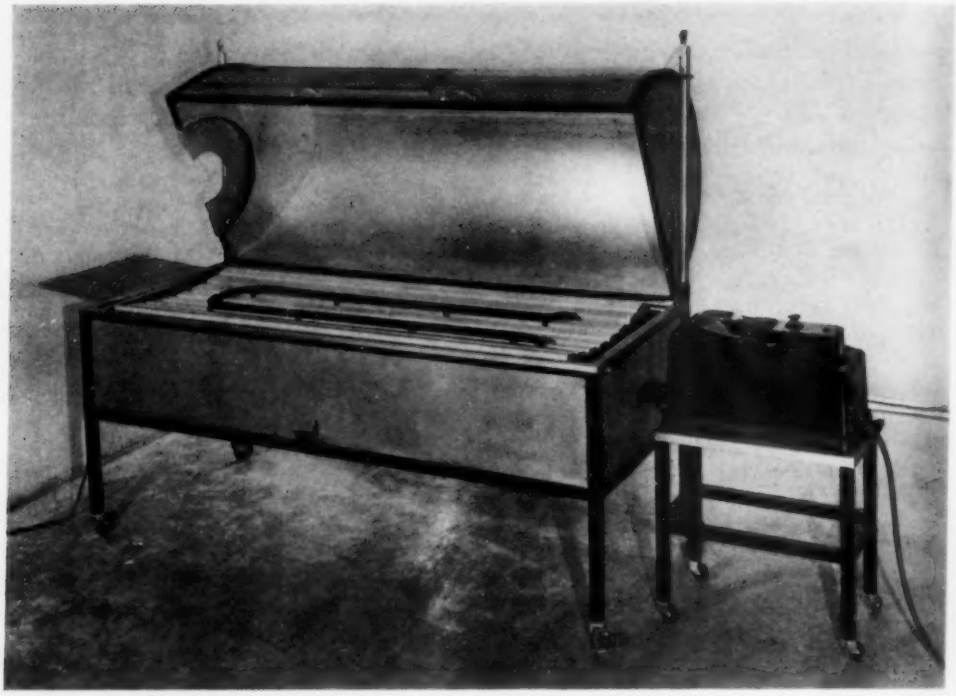


FIG. 3. The cabinet and pen showing the induction cable in place.

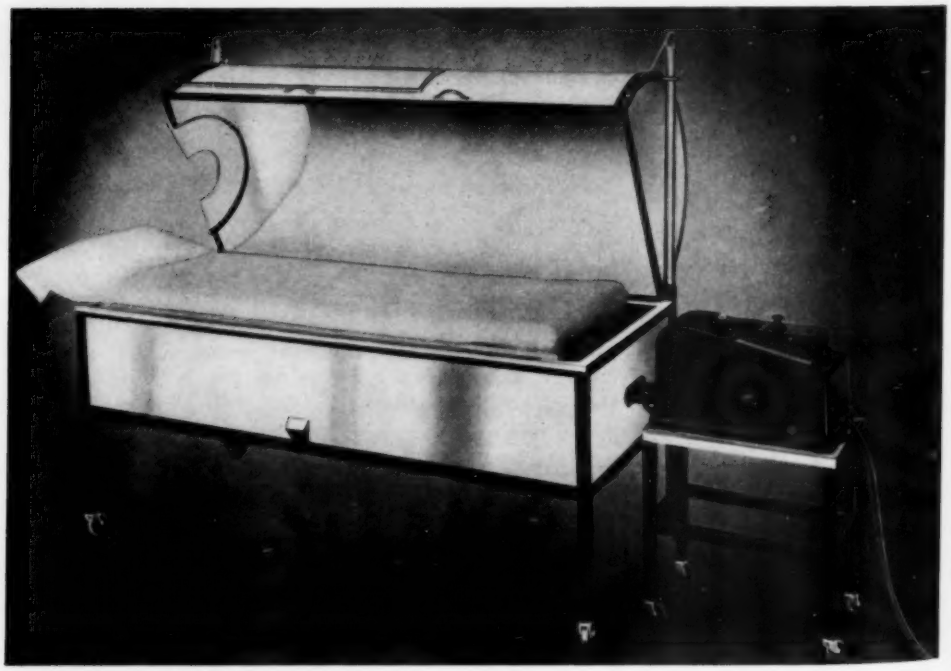


FIG. 4. The cabinet open and ready for the patient. The terry cloth to cover and wrap the patient in has been removed to show the airtex mattress covering the induction coil.

FIG. 5. The patient ready for treatment.

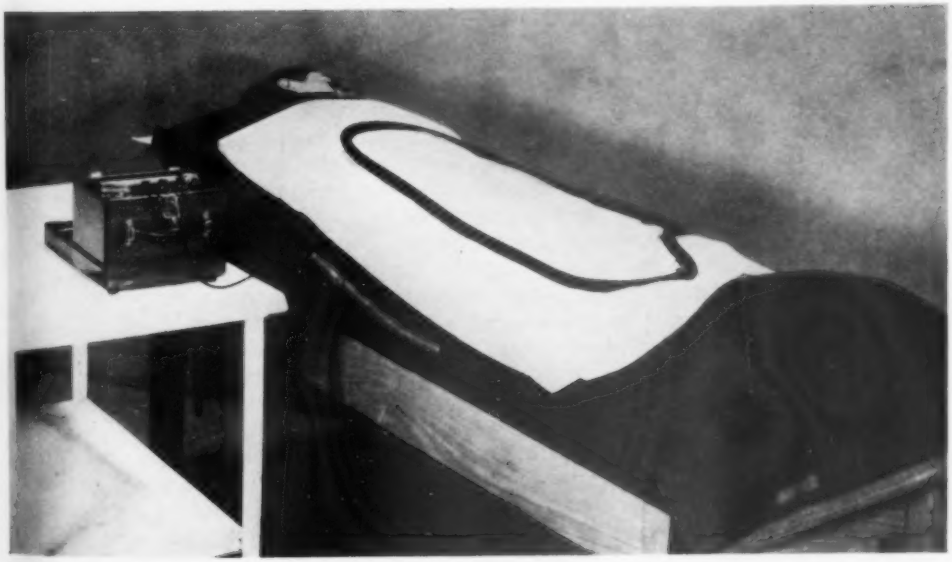


FIG. 6. Patient in zipper treatment bag with inductance cable in position ready for the electromagnetic current to be turned on. Note resistance thermometer (rectal) entering at small zipper pocket.

it should not be emphasized to the extent that the patient becomes unduly apprehensive. The patient or relatives should be told that such treatment is not without hazard, but when properly used the dangers are remote. The proper psychotherapy will do much to ally the patient's natural apprehension.

The contra-indications to this form of therapy must be considered.

Before accepting a patient for fever therapy he should be given a thorough physical examination which should also include an electrocardiographic and a routine clinical blood examination. If any doubt exists relative to the fasting blood sugar level, it is advisable to perform a glucose tolerance test in order to determine the possibility of impending hypoglycemic shock.

The patient should be given an enema the evening preceding the treatment, and the breakfast on the morning of treatment should be light, consisting largely of fluid foods or foods evacuated from the stomach within two hours. The use of drugs which inhibit perspiration, such as hyoscine, should be discontinued several days prior to the exhibition of fever therapy, and such drugs should never be given during treatment.

Some workers advise the use of sedatives before beginning the treatment. Schmidt [6] gives 15 to 30 grains of pentabromides in the form of the elixir, just before the treatment is started. He repeats this dose 30 minutes later. If the patient is still restless when the desired temperature level is reached, he gives pantapon, ⅓ gr. hypodermically. We do not use sedatives at the beginning of the treatment and only when absolutely necessary during treatment. We use from ⅛ to ¼ of a grain of morphine sulphate, and give it when the current is turned off. We endeavor in so far as possible not to use hypnotics. This matter is, however, an individual one, and nearly every fever therapist has his own particular views on the subject. However, drugs which tend to inhibit secretions, or produce peripheral vasodilation or excessive sweating, should not be used.

Once treatment has started, the nurse should be in constant attendance, and a physician within call. Her tact and understanding will do much to alleviate the patient's discomfort. The patient's face should be kept free of perspiration, and this is best done with a wet hand-towel. She should record the pulse, respiration, and rectal temperature every 15 minutes. The rectal temperature is taken by an ordinary clinical thermometer when electromagnetic induction is used, until the current is discontinued, and then for the remainder of the treatment an indicating resistance thermometer, as illustrated, is used. We feel that this instrument is invaluable because the patient's temperature may be kept under observation continuously and can be very accurately controlled at all times. The current is discontinued usually at approximately from one to two degrees Fahrenheit below the maximum temperature that is required. This is necessary because the patient's temperature will continue to rise from one to two degrees after the current is turned off. Usually the extent of the secondary rise can be gauged by the temperature increment with each 15 minute interval. The secondary rise is usually proportional to this increment so that with an increment of one degree or more the secondary rise will be much greater than when the 15 minute increments are below one degree Fahrenheit. The nurse should be instructed to keep the temperature within a certain range and for a given period of time. If the temperature consistently drops, it may be due to heat loss from some part of the insulation around the patient, particularly around the region of the neck. If the temperature has a tendency to rise, it frequently can be checked by applying a folded bath towel saturated with icewater and placed over the head and face in the form of a compress. Such a simple procedure will often maintain the desired temperature within a range of plus or minus 0.1° F. We also employ an electric fan to direct a current of air over the patient's head and face for short intervals, if the cold compress is not adequate. Occasionally it is necessary to open the side pocket of the treatment bag or the side panel of the cabinet. The nurse must, however, be familiar with the procedure necessary to cool a patient, when required.

During treatment, patients perspire freely, with a consequent water and chloride loss. To counteract any ill effects, we give patients a 0.6 per cent NaCl solution to drink—that is, 6 grams NaCl to one liter of water. This concentration is not particularly unpalatable. Three to four liters of fluid are usually taken in, during a treatment. If, however, a patient expresses a desire to have any other beverage, we usually give it, if available. With children we use fruit juices quite freely with some form of sugar added. It is well to administer the fluids frequently in small quantities to avoid gastric distention and nausea. Iced beverages should be avoided.

Whenever a bed pan or urinal is needed it should be preheated and given to the patient through the opening provided for that purpose, care being used to lose as little heat as possible through the opening. The electric current must always be switched off during the use of the bedpan in order to avoid the possibility of burns from the metal. A vague aching distress in the lower abdomen may be due to a distended urinary bladder, and voiding of urine may give prompt relief.

Friends or relatives should not be permitted to visit the patient during the treatment, since they often disturb and worry the patient. The room should be warm, well ventilated, and darkened so as to make conditions as conducive to sleep as possible. Noise and confusion should be carefully avoided. The physician referring the case for fever therapy should visit the patient after the fever has been induced, as this will often lend confidence and assurance to the patient. The physician under whose supervision the treatment is being given should visit the room frequently and show his interest in the outcome of the treatment. He should always be readily accessible during and for an hour after the treatment.

The nurse should be thoroughly familiar with all the warning signs which indicate that the temperature should be lowered or discontinued. Two potential dangers are omnipresent: one is a disturbance of the heat regulatory mechanism, resulting in heat stroke. This danger is intensified when high external temperatures surround the body. (Drugs which reduce perspiration excessively should not be used.) The other danger is circulatory collapse due to an unusual peripheral vasodilation, which results in an insufficient quantity of blood reaching the right side of the heart. For this reason no drug should be used as a hypnotic that has a tendency to produce engorgement of the peripheral blood vessels. The warning signals are the appearance of circumorbital pallor, marked irregularity of respiration, sharp drop, rise, or irregularity in rhythm and amplitude of the pulse rate. A marked diminution in perspiration is a major danger demanding continuous and careful attention; in such an instance it may be necessary to lower the temperature or even discontinue the treatment to safeguard the patient. The appearance of an almost imperceptible twitching of the muscles around the lips is an absolute sign contraindicating the continuance of the treatment, especially when treating chorea minor. When it becomes necessary to terminate treatment abruptly, covers are all removed from the patient, except for a light sheet across the pelvis, and the temperature is reduced as rapidly as possible by means of an electric fan directed across the body, and of ice cold applications restricted largely to the head, face, neck, and upper chest. A very effective means of stimulating respiration when necessary is to place one's hands in ice cold water and forcibly shake water from them on the patient's chest. When the temperature has fallen to a level of approximately 102° F. these radical procedures should be discontinued. The patient is then covered with a light blanket or sheet, and if the patient at any time complains of chilliness, he should be adequately covered. Probably the best method to combat circulatory collapse is to administer saline and glucose solution intravenously. Caffeine sodium benzoate is, we believe, the best heart stimulant to be used in these cases. In case of impending respiratory failure, the ideal procedure is to administer by a face mask, a mixture of 95 per cent oxygen and 5 per cent carbon dioxide as a respiratory stimulant.

When it is time to terminate the fever at the end of a successful treatment, all covers are removed from the patient. The patient is asked to inform the nurse as soon as he feels the least sign of chilliness, then the nurse covers the patient with a light covering such as a sheet or blanket. When the rectal temperature drops to 100° F., which usually requires from 30 minutes to two hours, the patient is given a tepid sponge bath, an alcohol rub, and returned to his room. Instructions are given to keep the patient in bed until the following morning, he being allowed any food he might desire. His temperature is taken hourly during the night to be sure that no secondary rise occurs.

Electropyrexia, since its introduction, has been used in the treatment of many conditions. Krusen [21] reported its use in no less than 50 different conditions during 1935. We shall confine discussion to those diseases in which electropyrexia appears to have decided merit.

General Paresis

Dementia paralytica was the disease first treated by electropyrexia, and the literature now contains the reports of 809 patients who have been treated here and abroad. Various authors have reported different remission rates. This, it would seem, indicates the necessity of following a definite standardized technic.

First, the selection of patients is important. Grandiose and expansive types with sudden onset have an excellent chance of reaching a perfect mental adjustment. Slowly dementing and depressed paretic patients are to be looked upon as more serious risks, and deteriorated paretic patients who have become demented to such an extent that they lead a purely vegetative existence, are hopeless, and should not be treated.

Second, the fever in the treatment of dementia paralytica should be maintained at a given height for a definite period of time. Bessemans [7] has determined the thermal death time of treponema pallidum both in vitro and vivo. As a result of his researches a fever above 103.5° F. for at least six hours, with an additional two hours at 105.8° F., has been used. Thus the fever is maintained for a period of at least eight hours. The two hours of high temperature is permitted at any point during the treatment, but is usually best tolerated at about the fourth and fifth hours. Treatments are given twice weekly, and usually 20 treatments constitute a course.

The serologic changes do not correspond to the amount of clinical improvement. A decrease in the number of cells usually occurs after a series of treatments. The Pandy reaction occasionally decreases in intensity; the colloidal gold reaction also tends to manifest improvement, and sometimes becomes practically negative. Often it is changed from a typical paretic to an atypical syphilitic-zone curve. The Wassermann test of the spinal fluid shows little change until many months have elapsed.

The spirochetes found in the central nervous system of human subjects are heat resistant and chemo-resistant organisms. The diseases which these organisms cause are eminently chronic. Therefore a program of treatment for any of these diseases to be effective must be drawn up with due consid-

eration of the chronicity of the disease and the increased resistance of the treponemas. Fever therapy should be followed by courses of tryparsamide combined with bismuth or mercury. This adjunctive treatment should be continued until the spinal fluid becomes and remains negative.

Arthritis

Definite clinical improvement has followed the use of foreign protein therapy in the treatment of arthritis. The fever which invariably accompanies such methods is frequently quite variable in degree as well as in duration. Therefore, in 1931 Markson and Osborne [8] introduced electropyrexia as a treatment of arthritis with the idea that much better and more lasting effects might be secured, if the fever was produced by a means subject to better control. We had reason to believe that the peripheral circulation might undergo definite and prolonged improvement. The use of the plethysmograph measuring finger volume changes by Johnson, Osborne and Scupham [9] supported this belief. Such was the rationale for its introduction.

Arthritis is a disease of obscure etiology, and often difficult to classify. As a result, we find many conflicting reports as to the value of fever therapy. We possess no common standard of criteria of improvement, which naturally complicates an evaluation of the therapeutic results.

It is believed that the therapeutic results depend to a large extent on the type of case selected. The hypertrophic, or degenerative type, should be excluded entirely because of the high incidence of associated cardiorenal damage present in these patients. They do not tolerate electropyrexia well and are subject to such accidents as myocardial failure and fibrillation. We select our patients solely from the infectious (atrophic) group, and this younger group of patients withstands fever without serious danger or discomfort.

There seems to have been no uniformity in regard to the degree and duration of the fever induced by various investigators. Our observations indicate that as a rule the fever induced should not be lower than 103.5° F. nor higher than 104° F. This generalization, however, does not hold when treating patients whose obvious reactions to such a temperature are poor as evidenced by a decided malaise from treatment to treatment. Hence, experience and clinical judgment are essential to the effective use of fever therapy.

The number of hours the fever was maintained has varied quite markedly. We have maintained temperatures of 103.5° to 104° F. for periods of four and of eight hours. Our best results have been secured with the eight hour period. The results secured with the four hour curve have not been as good nor were they maintained as well. Therefore we favor the use of an eight hour period, unless the patient's reactions indicate otherwise.

The treatment should be given once weekly and the number of treat-

ments to be given will vary with the individual. Our observations indicate that never less than eight treatments should be given, and that probably much better results may be obtained when an average of 20 are administered. Some investigators have given as few treatments as an average of three per patient. Hench[11] in 1936 summarized all published reports. He found that of a total of 315 patients with chronic atrophic arthritis treated by fever, only 5 per cent became symptom free; 25 per cent were notably relieved; and the remainder received little or no relief. We feel that if 30 per cent of these cases treated so diversely were notably relieved, the therapy is well worth while.

In our experience, the clinical improvement of these patients is not rapid but on the contrary is very gradual from week to week. The most marked improvement is usually evident about three months after a course of treatments. From this time on the improvement is often continued for some considerable time.

Arthritic patients who show evidence of poor vasomotor balance should be subjected to fever therapy with some degree of caution. Such patients are more liable to manifest shock and circulatory failure. The therapy is not contraindicated in these cases, but they should be treated with caution. Moreover, such patients should not be subjected to too rapid a cooling-off process at the termination of the treatment.

No single treatment has ever yielded the therapeutic results to be desired in arthritis, and one cannot expect that fever therapy alone will be sufficient. It would seem worth while to continue the use of other measures along with fever therapy, though such a policy obviously renders the evaluation of fever therapy difficult.

Gonorrheal Arthritis

Carpenter, Boak, Mucci and Warren[12] found the thermal death time of 130 strains of gonococci in vitro to vary from 106° to 107° F., the duration of the heat applied varying from six to 27 hours. A patient may be infected with more than one strain, but the patient and his consort will generally have the same strain. Strains showing a marked difference of thermal death time generally indicate a new infection superimposed on an old one. Articular strains are somewhat less resistant to heat than urethral strains. Therefore gonorrheal arthritis may subside before an associated urethritis. The ideal procedure in these cases, therefore, would be to ascertain the thermal death time of the organisms and to produce a corresponding degree of fever. Fever at 106° to 107° F. for five to 17 hours has been advocated by Warren, Carpenter and Boak.[13] They also claim that good results were obtained when a fever of three-fourths to one-half the thermal death time was given. Of course, the routine estimation of thermal death time is not always practical. A fever of 106.7° for five hours is frequently used and repeated if found necessary. Usually two to six treat-

ments are required and are given at from three to five day intervals. Hench [11] has published the following statistics on 182 cases reported in the literature. One hundred and twenty-eight cases or 70 per cent were more or less promptly "cured," becoming symptom free. About 15 per cent more were markedly improved and about 10 per cent received little or no benefit. Desjardins, Stuhler and Popp [14] state that it is more difficult to obtain cures in female than in male patients.

Bierman and Horowitz [15] have combined fever therapy with additional pelvic heating. They produced a fever of from 105° F. to 106° F., and then by means of a vaginal electrode secured a localized temperature of 111° F., which was maintained for three hours. They claim a cure for 19 of 23 patients treated in this manner.

Acute gonorrhea has been frequently treated with fever, but we believe that in the acute stage such a procedure is not indicated. Any form of therapy for gonorrhea which offers the slightest danger to life, is believed to be unwarranted.

Multiple Sclerosis

The most extensive observations on the treatment of multiple sclerosis with electropyrexia were carried out by Neymann and Osborne,[16] who reported their results on 25 patients. They classified their patients as mild, advanced, and far advanced. Forty-four per cent of the patients treated showed marked improvement, while an additional 40 per cent were improved to a lesser degree. They held out but slight hope of improvement in the far advanced types; the treatment of such patients entails a risk that one is hardly justified in taking.

The temperature in multiple sclerosis should under no circumstances be permitted to exceed 105° F., due to the danger of upsetting the heat regulatory mechanism and thus inducing heat stroke. A satisfactory fever for these patients is 103.5° F. for a period of from six to eight hours. The treatment should be terminated immediately, regardless of the duration of treatment, when the pulse exceeds 160 per minute, when the respiration is very rapid and shallow, or when marked cyanosis is present. With multiple sclerosis these danger signs demand prompt consideration and action on the part of the physician. Treatment is given once a week and the number of treatments required will vary, but will probably average between 20 and 30.

Asthma

Hyperpyrexia will not cure asthma, but it does have a very definite place in the treatment of asthma. Several reports have appeared since Feinberg, Osborne, and Afremow initiated the use of this procedure in 1931. Feinberg et al.[17] have summarized their results on 42 patients. They selected cases that had failed to respond to the usual methods of treatment and had been under their care for from a few months to several years. These severe

chronic and intractable asthmatics had one or more complicating pulmonary conditions such as emphysema, marked bronchitis or bronchiectasis. Fifty-one per cent of these patients manifested complete remission lasting from several days to 10 months; 29 per cent were improved without manifesting remission. These observers pointed out that remissions may be delayed for two or three weeks after treatment, and expressed the opinion that their results would probably have been more favorable if less severe cases had been selected.

Phillips [18] has recently made a study of 250 patients during an observation period of from six months to three years, but does not state his results.

These two groups of investigators used different technics. Feinberg et al. used a fever of 104° F., lasting for eight hours and given at a four-day interval, two treatments constituting a course. When the patient's condition did not permit such a fever, then a temperature of 103.5° was maintained for six hours. Improvement was observed even when only the lower fevers were employed.

The temperature should not exceed 105° F. The treatment should be given with the patient sitting in bed, reclining on a back rest; however, those who are able to be fully recumbent without discomfort are treated in that position. It is good practice to have a hypodermic syringe containing adrenalin immediately available so that it can be given without delay in case an attack is precipitated. Ice water or even very cold water should not be given because it may induce an attack.

Phillips [18] advocates the use of lower temperatures, from 101° to 102° F., given biweekly or weekly, the course amounting to at least 10 treatments. He maintains the temperature for from four to five hours.

Chorea Minor

The treatment for Sydenham's chorea has always been symptomatic. The disease has been recognized as being self-limited and as disappearing in from two to six months. Sutton and Dodge [19] have used typhoid vaccine for the purpose of producing therapeutic fever in patients with chorea, and reported excellent results. These workers have since used physical measures in preference to the foreign protein method. Following their work, Neymann, Blatt and Osborne,[20] using electropyrexia, have reported on the treatment of Sydenham's chorea. Of the 25 patients in their series, the disease was very severe in 9, moderately severe in 6, and comparatively mild in 10. The average period of hospitalization was less than 16 days, and the average number of treatments was less than four. The shortest period of hospitalization was five days with two treatments. These children were observed from five to 20 months after discharge from the hospital. Only three recurrences were observed.

Patients with acute carditis as a complication must be treated very cautiously. In such patients the first treatment should be of shorter dura-

tion and the temperature peak lower than in cases of uncomplicated chorea. The temperature in these cases should be maintained at 104° F. for eight hours. Temperatures of 105° F. or above should not be used because of the danger of convulsive seizures. The treatments can be given twice weekly.

The justification for subjecting patients having a disease with a tendency to cardiac involvement, to fever therapy is that if the recurrence of chorea can be prevented by this method of therapy, a crippling carditis may be prevented, since it is not only the first attack but also the subsequent attacks that affect the heart. In the second place it is desirable to shorten the number of hospital days or the period of confinement in the home, and the records of other investigators [22] in this field seem to demonstrate that these aims are accomplished.

The following table gives a summary of technic for treatment of the various diseases discussed.

TABLE II

Summary of Technic

Disease	Fever Curve		Approximate Number of Treatments	Frequency of Treatments	Selection of Cases
	Degrees F.	Duration in hours			
Arthritis	104 104	8 5	8–20	Weekly	Infectious (rheumatoid, proliferative)
Complication of gonorrhea	106.7	5	1–3	Weekly	G. C. arthritis, chronic urethritis, prostatitis, etc.
Asthma	104	6–8	2	2nd treatment 3 days later	Intractable Asthma
Multiple sclerosis	104	6–8	20	Weekly	Not too far advanced
General paresis	104 for 6 then increase 106 for 2		20	2 Weekly	Early paretic and not too badly demented patients
Sydenham's chorea	104	6–8	2–10	2 Weekly	Avoid cardiac complications unless well compensated

BIBLIOGRAPHY

1. MEHRTENS, H. G., and POUPOURIT, P. S.: Hyperpyrexia produced by baths, Neurol. and Psychiat., 1929, xxii, 700.
2. MERRIMAN, J. R., and OSBORNE, S. L.: Methods of producing hyperpyrexia by various physical agents, Ill. Med. Jr., 1933, lxiv, 237–241.
3. NEYMANN, C. A., and OSBORNE, S. L.: Artificial fever produced by high frequency currents, Ill. Med. Jr., 1929, lvi, 199.
4. NEYMANN, C. A., and OSBORNE, S. L.: The physiology of hyperpyrexia, Am. Jr. Syph. and Neurol., 1934, xviii, 18.

5. Gibson, J., Kopp, I., and Evans, W. A.: Paper read before First International Fever Conference, New York, 1937.
6. Schmidt, M., Holmquest, H. J., and Marshall, J. G.: Fever therapy. A simplified technic for inducing fever by electromagnetic induction, Physiotherapy Rev., 1936, xvi, 97.
7. Bessemans, A., and Thiry, U.: Nouveaux essais d'application de la thermotherapie locale au traitment de la syphilis primaire et secondaire chez l'homme, Bruxelles med., 1933, xiii, 299.
8. Markson, D. E., and Osborne, S. L.: The treatment of arthritis by sustained fever therapy, Ill. Med. Jr., 1931, lx, 397–403.
9. Johnson, C. A., Osborne, S., and Scupham, G.: Studies of peripheral vascular phenomena. The effect of artificial fever on the pulse volume changes of the fingers, Am Jr. Med. Sci., 1935, clxxxx, 485.
10. Nichols, E. H., and Richardson, F. L.: Arthritis deformans, Jr. Med. Res., 1909, xxi, 149–221.
11. Hench, P. S., Bauer, W., Fletcher, A. A., Ghrist, D., Hall, F., and White, T. P.: The problems of rheumatism and arthritis. Review of American and English literature for 1935. Third rheumatism review, Ann. Int. Med., 1936, x, 754–909.
12. Carpenter, C. M., Boak, R. A., Mucci, L. A., and Warren, S. L.: The studies on physiologic effects of fever temperatures; thermal death time of *Neisseria gonorrhea* in vitro with special reference to fever temperatures, Jr. Lab. and Clin. Med., 1933, xviii, 981–990.
13. Warren, S. L., Carpenter, C. M., and Boak, R. A.: The thermal death time of 130 strains of *Neisseria gonorrhea*. Report of 5th Ann. Fever Conference, May, 1935.
14. Desjardins, A. W., Stuhler, L. G., and Popp, W. C.: Fever therapy for gonococcic infections, Jr. Am. Med. Assoc., 1935, civ, 873.
15. Bierman, W., and Horowitz, E. A.: General hyperthermia with heat localization by radiothermy in the treatment of pelvic inflammatory disease, New York State Med. Jr., 1933, xxxiii, 218.
16. Neymann, C. A., and Osborne, S. L.: The treatment of some multiple sclerosis by electropyrexia, Jr. Nerv. and Ment. Dis., 1934, cxxix, 423–433.
17. Feinberg, S. M., Osborne, S. L., and Steinberg, M. J.: Sustained artificial fever in the treatment of intractable asthma, Jr. Am. Med. Assoc., 1932, lxxxxix, 801–806.
18. Phillips, K. M.: Hyperpyrexia in bronchial asthma, Arch. Phys. Ther., X-Ray and Rad., 1936, xvii, 282–288.
19. Sutton, L. P.: The treatment of chorea by the induction of fever, Jr. Am. Med. Assoc., 1931, lxxxxvii, 299–301.
Sutton, L. P., and Dodge, K.: The treatment of chorea by induced fever, Jr. Pediat., 1933, iii, 813–876.
20. Neymann, C. A., Blatt, M. L., and Osborne, S. L.: The treatment of chorea minor by means of electropyrexia, Jr. Am. Med. Assoc., 1936, cvii, 938–942.
21. Krusen, F. H.: The present status of fever therapy produced by physical means, Jr. Am. Med. Assoc., 1936, cvii, 1215–1221.
22. Transactions of International Fever Conference, New York, 1937.

THE PATHOLOGY AND MECHANISM OF ANAPHYLAXIS *

By VIRGIL H. MOON, *Philadelphia, Pennsylvania*

A SURVEY of recorded studies on anaphylaxis and on shock reveals the remarkable fact that neither of these conditions has been investigated by the methods of pathology. Probably this was because this type of circulatory phenomenon was interpreted as a functional disturbance having no morphologic basis. The belief that postmortem examinations in such conditions reveal no significant changes, apparently had not been questioned.

It has become apparent recently that a combination of the methods of pathology with those of physiology may produce pertinent evidence. It has been shown [17 a, b, 18] that shock, occurring clinically or produced experimentally in various ways, is associated with characteristic tissue changes which are etiologically related to the mechanism of its development. A similar study of anaphylaxis has revealed significant facts which give a broader comprehension of the mechanism of that phenomenon. In it, as in other conditions of disease, correct interpretations find corroboration in the accompanying morphologic changes. The discussions here will be limited to the mechanism of anaphylaxis, its morphologic features and its relationship to shock otherwise produced.

It is assumed that the reader is conversant with the various phases of anaphylactic phenomena, their conditions of occurrence, and related matters. Details of these will be found in reviews by Wells, Karsner, Zinsser, Topley and Wilson, and Seegal.

FUNCTIONAL DISTURBANCES

The signs of anaphylaxis in dogs are pruritus, increased respiratory rate, dyspnea, rapidly falling blood pressure, salivation, vomiting, diarrhea and urination. The vomitus is frothy and mixed with bile. In severe cases these discharges contain blood. The heart beats rapidly, even violently. There are ataxia, marked weakness, and sometimes convulsions. The pupils dilate and the eyes become dull. Death appears imminent but it seldom occurs within two or three hours and often is delayed 24 hours or longer. It has been found that immediate death may be produced in dogs by proper adjustment of the dosage.

The symptoms of human anaphylaxis or allergy are similar to those of dogs. In mild cases there are itching, restlessness, and the development of a skin rash or wheals. In severe cases there are generalized urticaria, erythema, dyspnea, cyanosis, edema of the face, tongue and throat, cough and

* Received for publication September 10, 1937.
From the Department of Pathology, Jefferson Medical College, Philadelphia.

expectoration of frothy sputum. Vomiting and defecation may occur. The blood pressure falls and the pulse becomes rapid and weak. Recovery or collapse and death may follow. In some cases asthmatic features are prominent. There is obvious similarity between these manifestations of anaphylaxis in dogs and man and those of shock produced by other means in these same species.

The bio-chemical and hematologic features which accompany anaphylaxis are essentially identical with those of traumatic or experimental shock. Seegal's review of this subject records the following changes in the chemistry of the blood of animals in anaphylaxis: The lactic acid and the sugar content are increased, likewise the urea, creatinine and non-protein nitrogen. The alkali reserve is decreased, the protease ferment is increased and its antiferment decreased (Jobling). Karsner's review states that the viscosity of the whole blood is increased and the sedimentation speed of the corpuscles decreased. Dean and Webb found a rise in the hemoglobin and red cell count following shock doses of horse serum into sensitive animals. The hemoconcentration was proportional to the severity of the symptoms. In severe reactions the blood chlorides are decreased (Major; Friedmann and Fränkel). The recorded observations on the blood sugar content in anaphylactic shock agree that it is increased. This applies to peptone poisoning as well.

The temperature first rises, then falls rapidly (Richet). But in prolonged, sublethal or chronic anaphylaxis the temperature increased in varying degrees. In serum sickness, in extensive necrosis or abscess following Arthus phenomenon, and in allergic reactions—" hay fever " for example—the temperature rises.

Dean and Webb found moderate leukopenia as represented by a reduction of the leukocytes to 25 per cent of the normal number. The maximum reduction was reached in about half an hour, and was followed by a marked leukocytosis. Richet found an intense leukocytosis ranging from 30,000 to 90,000 in 'chronic anaphylaxis,' i.e. those experiments in which death was delayed 10 to 48 hours. It is significant to note in this connection that Dale et al. found a marked leukopenia in fatal histamine shock while, in our own observations,[17 (3)] smaller injections of histamine were followed by leukocytosis in cats, monkeys and man. MacKenzie and Hanger's review on serum sickness records a moderate leukocytosis in that condition.

There is evidence of variations in coagulability similar to those reported in leukocytic counts. Seegal's summary shows that the coagulation of the blood is delayed in guinea pigs, dogs and rabbits. Shattuck recorded a similar finding in human cases of serum sickness and of chronic urticaria. He cited similar observations by Biedl and Krause and by Pepper and Krumbhaar. His observations indicated that this resulted from retarded prothrombin activity. Weil found that blood from dogs in anaphylactic shock would remain unclotted for many hours or even days. On the other hand, Witzinger and many others have shown that the *first injection* of

horse serum in man is followed by a marked *acceleration* in the speed of coagulation. This reaction finds a common clinical application in such injections for the control of persistent bleeding. Witzinger noted also that reinjection of horse serum after a delay of several days was followed by *retarded* coagulation time.

Each of the physiologic disturbances listed above occurs similarly in poisoning with peptone, in traumatic shock, and in anaphylaxis. Also in each of these, there are features which vary with the acuteness or stage of the condition: The coagulability of blood is high in early stages but decreases later; there is leukopenia in the severe early acute reactions followed by leukocytosis in later stages; an increase in temperature accompanies subacute reactions, but a fall in temperature occurs in severe or fatal cases. The similarity of these variations in traumatic shock, in poisoning with peptone and in anaphylaxis indicate a fundamental similarity in those conditions. There is lack of evidence concerning the mechanism which produces the variations.

Associated Pathologic Changes

I have made several detailed reports [17 (1, 2)] on the visceral changes found in shock. These were drawn from examinations of human cases following death from surgical or traumatic shock, burns, abdominal emergencies such as obstructions, perforations and acute pancreatitis, severe intoxications and other clinical conditions which led to circulatory collapse. Similar conditions were reproduced experimentally in dogs and identical circulatory changes were found post mortem in their viscera. These will be stated briefly for purposes of comparison with the visceral appearances found after death from anaphylaxis.

The respiratory and gastrointestinal mucosae are purplish-red, edematous and contain hemorrhagic flecks. The lungs are deeply congested, frequently they are edematous and contain ecchymoses. The pleurae, pericardium, peritoneum and meninges are congested, often they contain petechiae, and serous effusions are common. The liver and kidneys show diffuse congestion and acute parenchymatous degeneration. Capillary hemorrhages are seen in the brain and in other tissues. Characteristically the spleen is contracted and relatively bloodless.

The changes described result from atony and dilatation of the capillaries and venules which become relaxed, dilated and engorged with blood. This dilatation increases greatly the volume-capacity of the vascular system. The permeability of the endothelium becomes abnormally increased resulting in edema of tissues and in serous effusions. The leakage of plasma into the tissues increases the concentration and decreases the total volume of the blood. The combined effects of these processes produce a disparity between the blood volume and the volume-capacity of the circulatory system. This results in a progressive circulatory deficiency manifested in the syndrome of shock.

The earliest observations on anaphylaxis in animals record the same type of congestive, edematous and hemorrhagic changes in the viscera which we have found regularly in clinical and experimental traumatic shock. Portier and Richet (1902) noted in dogs: "There is intense congestion with interstitial hemorrhages in the whole gastrointestinal tract. The lungs are congested and sometimes also the endocardium and pleura." Gay and Southard (1908) found hemorrhages in one or more organs in 34 out of 41 guinea pigs following fatal anaphylaxis. These were most numerous in the gastrointestinal tract and the lungs, and were found occasionally in the adrenals, kidneys, pericardium and brain. They noted a similarity to the endotheliolysis produced by snake venoms. The authors regarded these findings as highly significant but did not advance any hypothesis concerning the origin of them. However, they emphasized that an acceptable explanation for anaphylaxis must also explain the congestive and hemorrhagic features observed. Coca (1909) noted congestion and many small hemorrhages in the lungs, and many dilated capillaries and venules were seen microscopically. Pearce and Eisenbrey (1910) described marked congestion of the viscera, numerous petechiae in serous surfaces and large ecchymoses in the gall-bladder and in the gastrointestinal mucosae following anaphylaxis in dogs. Weil confirmed the previous observations on visceral congestion and hemorrhages both in peptone poisoning and in anaphylactic shock in dogs. He noted parenchymatous degeneration, and in one instance marked necrosis, of hepatic cells. The livers in each instance were intensely congested, swollen and cyanotic.

Karsner (1912) studied the gross and microscopic changes in the lungs of guinea pigs following anaphylaxis. His observations were made on 52 animals sensitized to blood serum from various species. The gross and microscopic findings were of the same character in each group. Regularly the lungs were congested and contained hemorrhages. Microscopically they showed engorged capillaries, hemorrhages, and many of them were edematous. Conglutination thrombi such as usually accompany stasis were seen frequently in the minute vessels. These observations were made long before the significance of such changes accompanying shock was recognized. He drew no conclusions concerning the mechanism and significance of these circulatory changes.

Manwaring and his associates found pronounced splanchnic engorgement and cyanosis with hemorrhagic lesions in the intestinal mucosa both following peptone poisoning and following anaphylaxis in dogs. There were characteristic hemorrhagic lesions in the intestinal mucosae with edema of the intestinal villi followed by desquamation and superficial necrosis in the later stages. There was free blood in the lumina of the bowels. There was marked congestion but little hemorrhage after mild anaphylaxis. They believed that these effects were due to the action of a poison, formed in the liver, which had a histamine-like effect on the extrahepatic vascular structures. This effect accounted for the low blood pressure which

was regularly present. Similar circulatory changes were noted by Petersen and his associates, by Gurewitsch and by others.

We produced acute anaphylaxis in rabbits, guinea pigs and dogs in order to make observations on visible changes in the viscera. These confirmed the findings previously recorded. Visceral congestion, petechial hemorrhages and ecchymoses were present regularly when death occurred promptly, and the same features plus tissue edema when death was delayed. The following is a representative example:

A dog, weighing 8.4 kg., was sensitized by 5.0 c.c. of horse serum injected subcutaneously and three days later by 5.0 c.c. given intravenously. Fifteen days later 20.0 c.c. of horse serum were slowly injected intravenously. This produced immediate distress and severe illness. There were convulsions, the respirations became rapid and shallow and the pulse rapid and weak. The dog passed large quantities of liquid feces and of urine. There was a free flow of saliva. A period of apathy and collapse preceded death which occurred within 15 minutes after the injection.

Postmortem findings: The pleura and pericardium were moderately congested and the peritoneum extensively congested. No excess of fluid and no hemorrhages were present in the serous cavities. There were hemorrhages beneath the peritoneum about the ileo-cecal region. The minute vessels along the mesenteric attachment were engorged and unusually prominent.

The heart appeared normal except that its chambers contained almost no blood. The lungs were moderately congested as were also the mucosae of the trachea, bronchi and gall-bladder.

The liver was extremely congested. Blood dripped freely from the cut surfaces. The substance of the kidneys was similarly congested.

The mucosa of the stomach was moderately, and that of the duodenum was extremely congested. It had the appearance of purple velvet. The lumen of the small bowel contained blood tinged fluid. The lining of the large bowel and of the bladder were moderately congested. The spleen was dry, firm and bloodless. The pancreas and adrenals appeared normal.

On histologic examination the liver cells showed marked parenchymatous degeneration, some of them were necrotic, and the vessels were markedly engorged. There were extreme congestion and minute extravasations in the gastrointestinal mucosae. Moderate parenchymatous degeneration and congestion were seen in the renal cortex. The splenic pulp was relatively anemic.

Exactly similar changes were found in other dogs following anaphylaxis. It was noted that when death occurred within a few minutes no edema was seen, whereas after delayed death edema was regularly present in the lungs, respiratory mucosae and in the gastrointestinal lining. Frequently there were petechial hemorrhages in the mucous and serous surfaces and occasionally there was fluid in serous cavities. These observations were made in rabbits, guinea pigs and dogs. The same changes resulted from injections of peptone, extracts of various normal tissues and from histamine. At this point it should be emphasized that the changes described are characteristic of shock produced experimentally by various means.

Similar evidences of circulatory disturbance are recorded following death from serum injections in man. In the case reported by Boughton, death resulted in 45 minutes after the injection of one minim of horse

serum into a hypersensitive person. The necropsy examination revealed intense injection of the minute vessels throughout the abdominal viscera, especially in the stomach, small bowel, mesentery, gall-bladder and appendix. The parietal peritoneum was markedly congested. Both lungs were emphysematous and contained areas of hemorrhage. There were petechiae in the pericardial surfaces and the kidneys were markedly hyperemic. The microscopic examination showed pulmonary hyperemia and hemorrhages, hyperemia, hemorrhages and edema of the kidneys, small hemorrhages in the myocardium and adrenals, and edema of the hepatic cells.

Lamson's review of cases of sudden death following injection of foreign proteins contains only a few details of postmortem examinations. Congestion of the brain, meninges, liver, kidneys, gastrointestinal mucosae, general stasis, emphysema and congestion of the lungs were the changes noted. Bullowa and Jacobi reported the necropsy findings in a child after an injection of anti-diphtheritic serum. The blood in the great vessels was unclotted and was small in amount. There was marked congestion of the cerebral surfaces, the meninges, lungs, liver, adrenals, kidneys and spleen. Parenchymatous degeneration of hepatic cells was noted.

I have had opportunity to make postmortem observations in only one case of this kind. A negro youth 18 years of age developed meningitis of the epidemic type and was given antimeningococcic serum intravenously. He promptly developed respiratory distress, and circulatory failure was followed by death in a few minutes. There was no history obtainable regarding any previous injection of horse serum. The necropsy was made by Dr. D. R. Morgan who kindly allowed me to examine the organs. There were intense congestion, edema and hemorrhages in the lungs, respiratory mucosae and lining of the gastrointestinal tract, also intense congestion of the liver and kidneys. The spleen was small, flabby and relatively bloodless.

From the available evidence it appears that the indications of circulatory disturbance seen in the tissues after death from anaphylactic shock are of the same character and distribution as those after experimental or clinical traumatic shock. One is led to believe that the mechanism of circulatory disturbance and death in these conditions is similar.

The Mechanism of Anaphylaxis

Two interpretations have been considered as explanations for the phenomena associated with anaphylaxis. The earlier interpretation was that the reaction between antigen and antibody occurs in the circulating blood and/or in the tissue fluids, and gives rise to a toxic substance—' anaphylatoxin '—whose effects on various cells of the body produce the characteristic syndrome. Several serious objections have rendered this theory untenable. The incubation of antibody with antigen in vitro does not produce a potent injurious product. The precipitate resulting from such a combination is

relatively innocuous. The simultaneous injection of antibody and antigen does not produce shock in nonsensitized animals. In passive sensitization an interval of several hours must elapse before the injection of the antigen will produce characteristic symptoms. Evidently such results are not explainable as taking place in the blood itself.

Other evidence incompatible with the anaphylatoxic theory was supplied by Gay and Southard (1908). They showed that if all the blood from a sensitized animal is replaced by blood from normal animals of the same species, the animal still remained sensitive. The injection of antigen into such an animal produced characteristic anaphylactic reactions. This observation was confirmed by others. Schultz showed that organs whose vessels had been washed clean of blood by perfusion with salt solution, still responded characteristically to the introduction of the antigen. A bit of excised uterine musculature from an animal sensitized to horse serum will contract vigorously when a minute amount of horse serum is added to the fluid in which the strip of muscle is suspended. Muscle from a non-sensitized animal gives no such response when similarly treated. This reaction, confirmed by Dale, Weil and others, has become a standard method for determining sensitivity.

These facts together with others led to the interpretation that the reactions which produce the manifestations of anaphylaxis take place, not within the body fluids but within the tissue cells. That the reactions are not due to any toxicity of the antigen-antibody combination itself, or of its derivatives, but to disturbances within tissue cells arising from the combination of antigen and antibody within or upon them.

Cells are irritated when antigen and antibody meet within them. The resulting disturbances of function vary with the physiology of the cells within which they meet. Smooth muscle cells contract, as shown in the classic test for sensitivity in which guinea pig uterine muscle is used. Mucous cells discharge their secretion, as shown when antigen is applied to the membranes of a sensitized animal. The gastrointestinal mucosae discharge mucus and fluid more freely, as shown in the diarrhea which often accompanies anaphylaxis. Glands secrete more actively, as indicated by the excessive salivation which accompanies anaphylaxis in dogs. Petersen and his associates believed that the active mobilization of enzymes, which is associated with anaphylaxis, originates from the stimulated or injured cells such as endothelium, liver, pancreas and others. Capillaries lose their tonus and the endothelium becomes more permeable when subjected to anaphylactic irritation. This was shown by perfusion experiments (Manwaring) and by the development of tissue edema both in systemic and in local anaphylaxis. Opie interpreted the extensive edema which develops in anaphylaxis as due to the meeting of antigen and antibody within the endothelial cells. The resulting injury caused increased permeability of the capillary walls.

Severe anaphylactic irritation to the cells results in parenchymatous

changes as shown in the myocardium, liver and kidneys by histologic examination. When the irritation is more severe, necrosis results and the Arthus phenomenon is produced. An inflammatory reaction, noted by many and studied particularly by Opie, results when antibody meets its antigen in the tissues.

The systemic disturbances are manifestations of the sum total of the cellular effects. These vary in different species and seem to depend upon the type of cells most affected in a particular species. In guinea pigs the chief manifestation results from broncho-spasm, in rabbits vasculo-spasm, and so on. But in *each species* there is evidence also of *endothelial* injury. Seegal's review of the subject led her to conclude that most of the symptoms of anaphylactic shock in the various animals, are referable to one or the other of two causes: *contraction of smooth muscle* and *increased capillary permeability.*

Petersen and his associates noted an increased flow of lymph when dogs sensitized to egg albumin received that substance by injection. This lymph was rich in fibrin, globulin and albumin which indicated that it resulted from leakage through capillary walls. No increased flow of lymph followed the injection of egg albumin into non-sensitized dogs. They interpreted this as definite evidence of endothelial injury which took place immediately following the injection, and as evidence that the endothelium is the point of attack of the injuring agent in anaphylaxis. If recovery took place the endothelium became less susceptible to subsequent injections and a refractory state resulted. They concluded that shock of the endothelium is a primary factor in producing the symptoms of acute anaphylaxis.

Manwaring and his associates stressed the importance of the liver as the seat of anaphylactic injury in dogs, but their final interpretation was stated as follows: " We believe that the increased capillary permeability thus demonstrated will ultimately be shown to be the dominant physiologic change in protein sensitization, to which all other anaphylactic reactions are secondary."

Lewis emphasized capillary permeability as the major factor in anaphylaxis and attributed it to the release of H-substance by tissue cells injured by the combination of antigen-antibody. It is questionable whether this explanation applies to all instances in which urticaria develops. Without questioning the validity of his conclusions concerning the 'triple response' following mechanical and other forms of injury to tissue cells, I propose an alternate explanation for the urticaria of protein sensitivity. Lewis explains it as resulting from the injurious effects of the antigen upon the sensitized *tissue* cells which, in response to that injury, release H-substance thereby producing the triple response. The alternate explanation is that *not only* the *tissue* cells but also the *capillary endothelial* cells are sensitized and consequently are directly injured by contact with the antigen. These two concepts are presented visually in the accompanying diagram.

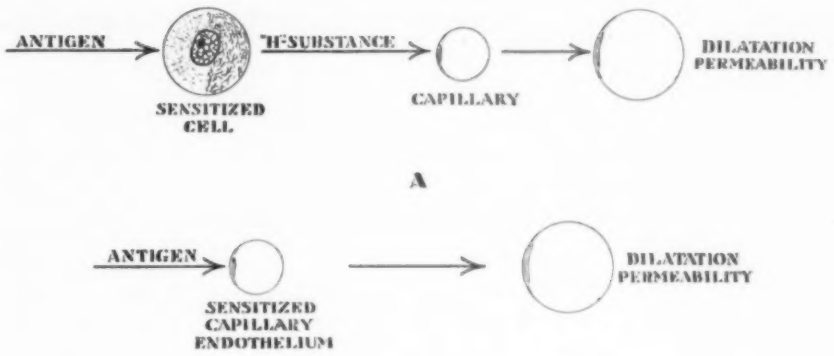


FIG. 1.

(*A*) Illustrates the mechanism proposed by Lewis. Antigen acting on *sensitized cells* causes the release of H-substance which causes adjacent capillaries to dilate and to become permeable.

(*B*) Illustrates the direct effect of antigen upon *sensitized capillary endothelium* with the same result.

If the mechanism were indirect, as believed by Lewis, anaphylaxis should be gradual in onset. Horse serum injected intravenously does not come in contact with tissue cells immediately. Normal capillary endothelium is relatively impervious to serum, and most of it remains for a relatively long time in the blood. Field and Drinker were able to detect traces of horse serum in the lymph of dogs, only after an interval of one or two hours following its intravenous injection. The full effect of an injection of horse serum into a sensitized animal would not be felt until the serum had slowly penetrated the capillary membranes and had entered the tissue cells.

The explosive promptness of anaphylaxis in a highly sensitized animal suggests a *direct,* rather than indirect, mechanism. I have seen death occur within 10 minutes following the intravenous injection of horse serum into sensitized dogs. Lamson's review of anaphylactic deaths in man showed that in 40 such cases, death occurred within an hour in 33, within 15 minutes in 28 and within 5 minutes in many cases. Wells cited a case in which a man, who previously had received injections of tetanus antitoxin, was transfused from a donor who that very morning had received an injection of anti-toxic serum. Death occurred within a few seconds. Such reactions are too prompt to be explained satisfactorily by the indirect mechanism proposed by Lewis. The view that such results are from the *direct* effect of antigen upon *sensitized endothelium* is in perfect consonance with the accepted interpretation that the tissue cells constitute the seat of the anaphylactic reaction. The view merely *includes endothelial cells* among the tissue cells affected.

Wheals, Inflammation and Shock

It is pertinent at this point to emphasize an essential physiologic relationship between wheal formation (the 'triple response' of Lewis), inflammation and shock. I have been unable to find a single exception to the following generalization: *Those agents which when applied to the skin evoke an urticarial reaction, will likewise evoke acute inflammation when applied to normal tissues. The same agents will produce typically the syndrome of shock if their effects are exerted systemically.* For examples: mechanical trauma to the skin is followed by wheal formation (Lewis), if more extensive it is followed by inflammation; severe extensive mechanical trauma results in shock. Histamine produces a wheal when a minute amount is applied in the skin, and produces acute inflammation when introduced intc living tissues; when a sufficient quantity is injected intravenously, shock is the result. Heat suitably applied to the skin produces the 'triple response,' and is followed by inflammation; an extensive superficial burn will cause shock. A minute amount of antigen produces a wheal in the skin of a sensitized subject and will produce local inflammation (Arthus' phenomenon) of the tissues under suitable conditions; the injection of a sufficient amount of protein into a subject sensitized to it, will produce shock. The same observations apply to a wide variety of agents including chemical poisons such as $HgCl_2$, arsenicals et al., sepsine, emetine, peptone and extracts of tissue, bile and cholic salts, the poisons of actinia and other marine animals, bee-sting poison, snake venoms, diphtheria toxin and other bacterial products.

The essential factor in the reaction to all such agents is injury to capillary endothelium produced either directly or, as postulated by Lewis, indirectly through the agency of a substance released by the tissue cells in response to the injury. Wheal formation results from the local effects of vascular dilatation and permeability. These are the circulatory changes of acute inflammation. The leukocytic phenomena of inflammation are produced by substances liberated by injured cells.[17] [3] When similar dilatation and permeability of capillaries and venules are produced in extensive visceral areas, they result in a circulatory deficiency which manifests itself in the syndrome of shock.

Summary

The physiologic disturbances accompanying anaphylaxis are of the same character as those of poisoning with peptone, and those of traumatic shock. The gross and microscopic visceral changes are of the same character after death from each of these conditions. These observations indicate that the underlying mechanisms are related.

The anaphylactic reaction is cellular rather than humoral in location. The meeting of antibody and antigen within the cells irritates or injures them and causes increased functional activity if the injury is mild. If

severe it results in an inflammatory reaction not different from that which follows other injuries.

There is evidence that the capillary endothelium is a chief point of injury in anaphylaxis. The capillaries respond to this, as to other injuries, by loss of tonus and increased permeability. Anaphylactic shock probably results from the direct effect of the antigen upon the sensitized endothelial cells, rather than indirectly by injury to tissue cells which by liberating H-substance cause capillary dilatation.

The development of skin wheals, tissue inflammation and systemic circulatory failure in anaphylaxis, is significantly similar to wheals, inflammation and shock following trauma and other injuries to living tissues. The fundamental capillary reactions in these respective phenomena are identical.

BIBLIOGRAPHY

1. Boughton, T. H.: Anaphylactic death in asthmatics, Jr. Am. Med. Assoc., 1919, lxxiii, 1912.
2. Bullowa, J. G. M., and Jacobi, M.: Fatal human anaphylactic shock; report of case with autopsy, observations and review of literature, Arch. Int. Med., 1930, xlvi, 306–315.
3. Coca, A. F.: Die Ursache des plötzlicken Todes bei intravenöser Injektionen artfremder Blutkorper, Virchow's Arch., 1909, cxcvi, 92.
4. Dale, H. H.: The anaphylactic reaction of plain muscle in the guinea pig, Jr. Pharm. and Exper. Therap., 1912, iv, 167.
5. Dean, H. R., and Webb, R. A.: Blood changes in anaphylactic shock in dog, Jr. Path. and Bacteriol., 1924, xxvii, 65–79.
6. Field, M. W., and Drinker, C. K.: Permeability of capillaries of dog to protein, Am. Jr. Physiol., 1931, xcvii, 40–51.
7. Friedmann, U., and Fränkel, E.: Ueber Veranderungen der Wasser- und Kochsalz ausscheidung während der Serumkrankheit, Verhandl. d. deutsch. Gesellsch. f. inn. Med., 1921, xxxiii, 400.
8. Gay, F. P., and Southard, E. E.: Further studies in anaphylaxis, Jr. Med. Res., 1907, xvi, 143; 1908, xix, 17.
9. Gurewitsch, N. A.: Über den reflektorischen und den toxischen Gefässshock, Arch. f. clin. Chir., 1931, clxvi, 401–411.
10. Jobling, J. W., Petersen, W. F., and Eggstein, A. A.: The mechanism of anaphylactic shock, Jr. Exper. Med., 1915, xxii, 401.
11. Karsner, H. T.: The lungs of the guinea pig in anaphylaxis produced by toxic sera, Immunitätsforsch. u. exper. Therap., 1912, xiv, 81. Bacteriology and immunology, 1928, chapter lxxiii, Jordan and Falk, University of Chicago Press.
12. Lamson, R. W.: Sudden death associated with injection of foreign substances, Jr. Am. Med. Assoc., 1924, xcii, 1091–1098.
13. Lewis, T.: Blood vessels of the human skin and their responses, 1927, Shaw and Sons, London.
14. Mackenzie, G. M., and Hanger, F. M.: Serum disease and serum accidents, Jr. Am. Med. Assoc., 1930, xciv, 260.
15. Major, R. H.: Studies of blood chemistry in allergy, Bull. Johns Hopkins Hosp., 1923, xxxiv, 104–108.
16. Manwaring, W. H., Chilcote, R. C., and Hosepian, V. M.: Capillary permeability in anaphylaxis, Jr. Am. Med. Assoc., 1923, lxxx, 303–309.
17. Moon, V. H.: (1) The shock syndrome in medicine and surgery. (2) Shock, a definition and differentiation. (3) Mechanism of acute inflammation, Ann. Int. Med., 1935, viii, 1633: Arch. Path., 1936, xxii, 325; ibid., 1935, xx, 561.

18. Moon, V. H., and Kennedy, P. J.: Pathology of shock, Arch. Path., 1932, xiv, 360–371.
19. Opie, E. L.: Desensitization to local action of antigen (Arthus phenomenon), 1924, ix, 247–268. Inflammation and immunity. Jr. Immunol., 1929, xvii, 329–342.
20. Pearce, R. M., and Eisenbrey, A. B.: Anaphylactic shock in the dog, Jr. Infect. Dis., 1910, vii, 565.
21. Petersen, W. F., Jaffe, R. H., Levinson, S. A., and Hughes, T. P.: Endothelial permeability; endothelium in canine anaphylactic shock, Jr. Immunol., 1923, viii, 323–349: Jr. Biol. Chem., 1925, lxiii, 179.
22. Portier, P., and Richet, C.: De l'action anaphylactique de certains venins, Compt. rend Soc. d. biol., 1902, liv, 170.
23. Richet, C.: Anaphylaxis, 1913, Liverpool University Press.
24. Schultz, W. H.: Physiologic studies in anaphylaxis, Jr. Pharm. and Exper. Therap., 1912, iii, 299.
25. Seegal, B. C.: Agents of disease and host resistance, by Gay, F. P. et al., 1935, Thomas, Baltimore, chapter vi.
26. Shattuck, H. F.: Protein intoxication, Arch. Int. Med., 1917, xx, 167.
27. Topley, W. W. C., and Wilson, G. S.: Principles of bacteriology and immunology, 1936, Wm. Wood and Co., Baltimore.
28. Weil, R.: (1) The nature of anaphylaxis and the relations between anaphylaxis and immunity. (2) Studies in anaphylaxis, Jr. Med. Res., 1912, xxvii, 497; 1914, xxx, 87, 299. Anaphylaxis of dog, Jr. Immunol., 1917, ii, 399, 525.
29. Wells, H. G.: Present status of problems of anaphylaxis, Physiol. Rev., 1921, i, 44. Chemical pathology, 1925, W. B. Saunders, Philadelphia, p. 220–235.
30. Witzinger, O.: Zur anaphylaktischen Analyse der Serumkrankheit, Ztschr. f. Kinderheilk., 1911, iii, 211.
31. Zinsser, H.: Resistance to infectious diseases, 1931, 4th ed., Macmillan, New York.

EXPERIENCES IN TREATING TOXIC GOITER IN A LARGE PUBLIC HOSPITAL *

By W. O. Thompson, M.D., F.A.C.P., S. G. Taylor, III, M.D., K. A. Meyer, M.D., and R. W. McNealy, M.D., *Chicago, Illinois*

The treatment of disease in a large public hospital presents unique problems. The Cook County Hospital, in which this study was made, has 3200 beds and its patients represent, for the most part, the poorest element in the city of Chicago. The conditions in the hospital with regard to the staff, interns, nurses, diet and crowding are about the same as in most similar institutions. Disease is seen more in its advanced than in its early stages; and in the case of toxic goiter, a large number of severe cases of long standing are observed in markedly undernourished individuals. It is of interest to observe whether these factors preclude the establishment of a low operative mortality rate in this disease.

The mortality from operations for goiter in this hospital has been summarized in a previous communication to this College.[1] For the years 1931, 1932 and part of 1933 it was 13.1 per cent for exophthalmic goiter, 9.8 per cent for toxic adenoma, 4.1 per cent for non-toxic adenoma and 2.6 per cent for simple goiter. Among factors responsible for these high mortality rates may be mentioned (1) inadequate preoperative and postoperative care, with lack of good judgment in selecting the time of operation, and (2) too frequent relegation of operative procedures to surgeons who lacked the special training requisite for thyroid surgery. It was common practice for patients to be operated on from seven to ten days after starting iodine, regardless of other considerations. Patients were placed on the usual ward diet which was, for them, very inadequate in calories, and they often lost weight on it. The time of operation was often decided, not by the attending man, but by the senior intern. The infrequency of checking the condition of the patient with metabolism tests may be gauged from the fact that there was one unsatisfactory basal metabolism machine for the whole hospital of 3200 beds, and that only a few tests were done each day by a technician who also had the responsibility of the electrocardiographic laboratory. The fluid used for parenteral administration, because of its method of preparation, usually produced severe reactions, almost uniformly causing chills, fever, and redness and swelling of the part into which it was injected. In some instances records indicate that reactions from fluid may have contributed to the death of the patient, particularly when given intravenously.

* Read before the Twenty-Second Annual Session of the American College of Physicians, New York, April 8, 1938.

From the Department of Medicine, Rush Medical College of the University of Chicago, the Department of Surgery, Northwestern University, and the Cook County Hospital, Chicago.

We began our work in the latter part of 1932. It was neither possible nor desirable that we should have control of all the patients with goiter in the hospital. From 1933 on we observed nearly half of them. The remainder served as a control for a few years, and later on in modified degree, after the ideas developed exerted some influence throughout the whole hospital. We are very grateful to the various members of the staff who cooperated with us to make this study possible. The hospital has made an important contribution by permitting us, with few exceptions, to keep patients in the institution as long as seemed desirable to prepare them for operation.

We began by treating each patient as an individual problem. Perhaps the most important principle adopted was the withholding of surgery until the condition of the patient justified operation, regardless of how long this took. It is our contention that the battle is commonly won or lost before any operative procedures are carried out and that in most instances a crisis in the postoperative period means inadequate preoperative preparation. We have not been greatly concerned with the length of time that iodine was administered before operation, often extending it to many weeks in spite of an increase in basal metabolism. In general, the other factors concerned offset this risk. Until the fluid for parenteral use was improved, we prohibited its administration unless specially prepared fluid was obtained outside the hospital.* A special high caloric diet for patients with toxic goiter was developed and operation was rarely resorted to unless the patients gained weight. Another important consideration was that we gradually gained more control over the selection of surgeons.

Results

It will be necessary to group toxic adenoma and exophthalmic goiter together under the general heading "toxic goiter." In our own series a distinction was made between the two diseases, but in the case of other observers, the diagnosis of toxic adenoma was made too frequently, usually by the intern. We have gone through all the hospital records for the years 1931–33 and tried to establish the true proportion of toxic adenoma to exophthalmic goiter for these years. So far as we could tell, it was about 1 case of toxic adenoma to 3 of exophthalmic goiter (1 to 3½ in our own series), and this ratio probably holds throughout succeeding years.

We have summarized the mortality rates in patients who were under our care and those who were not, in tables 1 and 2 and in figure 1. In 1931, just before our work began, there were 16 deaths following 159 thyroidectomies for toxic goiter—a mortality of 10.1 per cent. During the period

* Some time after the work was started we began distilling small amounts of water for the preparation of fluid for parenteral use in our own laboratory, and for many months this was the only source in the hospital of water suitable for such purposes. This function was later taken over by Dr. Fantus. Making good fluid available to all the patients in the hospital has, in our opinion, been one of the major therapeutic improvements of the last few years.

TABLE I

Mortality from Thyroidectomy, Cook County Hospital—Our Series

Year	Toxic Goiter (All Cases)				Exophthalmic Goiter				Toxic Adenoma			Non-Toxic Goiter			All Types		
	Number of Patients	Number of Operations	Number of Deaths	Operative Mortality Per cent	Number of Patients	Number of Operations	Number of Deaths	Operative Mortality Per cent	Number of Operations	Number of Deaths	Mortality Per cent	Number of Operations	Number of Deaths	Mortality Per cent	Number of Operations	Number of Deaths	Mortality Per cent
1932...	8	8	0	0.0	6	6	0	0.0	2	0	0.0	1	0	0.0	9	0	0.0
1933...	64	69	2	2.9	55	60	2	3.3	9	0	0.0	12	0	0.0	81	2	2.5
1934...	47	52	4	7.7	40	45	4	8.9	7	0	0.0	6	0	0.0	58	4	6.9
1935...	62	65	0	0.0	42	45	0	0.0	20	0	0.0	28	0	0.0	93	0	0.0
1936...	68	71	3	4.2	46	49	2	4.1	22	1	4.5	22	0	0.0	93	3	3.2
1937...	51	52	0	0.0	39	40	0	0.0	12	0	0.0	19	1	5.3	71	1	1.4
1932–37	300	317	9	2.8	228	245	8	3.3	72	1	1.4	88	1	1.1	405	10	2.5
1932–34	119	129	6	4.7	101	111	6	5.4	18	0	0.0	19	0	0.0	148	6	4.1
1935–37	181	188	3	1.6	127	134	2	1.5	54	1	1.9	69	1	1.4	257	4	1.6

1932–37 there were 54 deaths following 572 thyroidectomies for toxic goiter in patients whom we did not have charge of—a mortality of 9.4 per cent. During the same period there were 9 such deaths following 317 thyroidecto-

TABLE II

Mortality from Thyroidectomy, Cook County Hospital—Series of Other Observers

Year	Toxic Goiter			Non-Toxic Goiter			All Types		
	Number of Operations	Number of Deaths	Mortality Per cent	Number of Operations	Number of Deaths	Mortality Per cent	Number of Operations	Number of Deaths	Mortality Per cent
1931.....	159	16	10.1	36	2	5.6	195	18	9.2
1932.....	149	19	12.8	48	1	2.1	197	20	10.2
1933.....	85	12	14.1	47	2	4.3	132	14	10.6
1934.....	89	4	4.5	69	4	5.8	158	8	5.1
1935.....	102	8	7.8	56	0	0.0	158	8	5.1
1936.....	72	5	6.9	45	1	2.2	117	6	5.1
1937.....	75	6	8.0	25	0	0.0	100	6	6.0
1931–37...	731	70	9.6	326	10	3.1	1057	80	7.6
1932–37...	572	54	9.4	290	8	2.8	862	62	7.2
1932–34...	323	35	10.8	164	7	4.3	487	42	8.6
1935–37...	249	19	7.6	126	1	0.8	375	20	5.3

mies for toxic goiter in patients whom we did have charge of—a mortality of 2.8 per cent. The number of cases is not large enough for the mortality rates to be significant on a yearly basis, but they naturally divide themselves into two groups (*a*) those up to the end of 1934, and (*b*) those in the period 1935–37. In February 1935 a new ward was opened in the hospital in which about 10 beds were allotted to us for the study of patients with goiter. Since that time we have had better control over the preoperative and postoperative care of our patients and have been able for the most part to restrict operations to a few men with a special interest and training in thyroid surgery. In the earlier period, 1932–34, there were 35 deaths following 323 thyroidectomies for toxic goiter in patients who were not under our care—a mortality of 10.8 per cent: and during the same period there were 6 deaths following 129 such operations in patients who were under our care—a mortality of 4.7 per cent. In the later period, 1935–37, there were 19 deaths following 249 thyroidectomies for toxic goiter in patients not under our care—a mortality of 7.6 per cent; whereas following 188 such thyroidectomies in patients under our care, there were 3 deaths—a mortality of 1.6 per cent. In other words, our mortality has been less than one-fourth as great as in the rest of the hospital during the later period, and less than one-third as great during the whole period 1932–37.

During the first period when the mortality rate for all our cases of toxic goiter was 4.7 per cent as compared with 10.8 per cent for other observers, we were able to control the preoperative and postoperative care to a considerable extent, but had very little choice of surgeons. During the

second period, when our mortality rate was 1.6 per cent compared with 7.6 per cent among other cases, we were able to control the preoperative and postoperative care still better, had developed more conservatism about the time of operation, and were able to restrict the operations to a smaller number of more experienced surgeons. Thus, our mortality of 1.6 per cent in the second period of the study may be compared with the mortality of 10.8

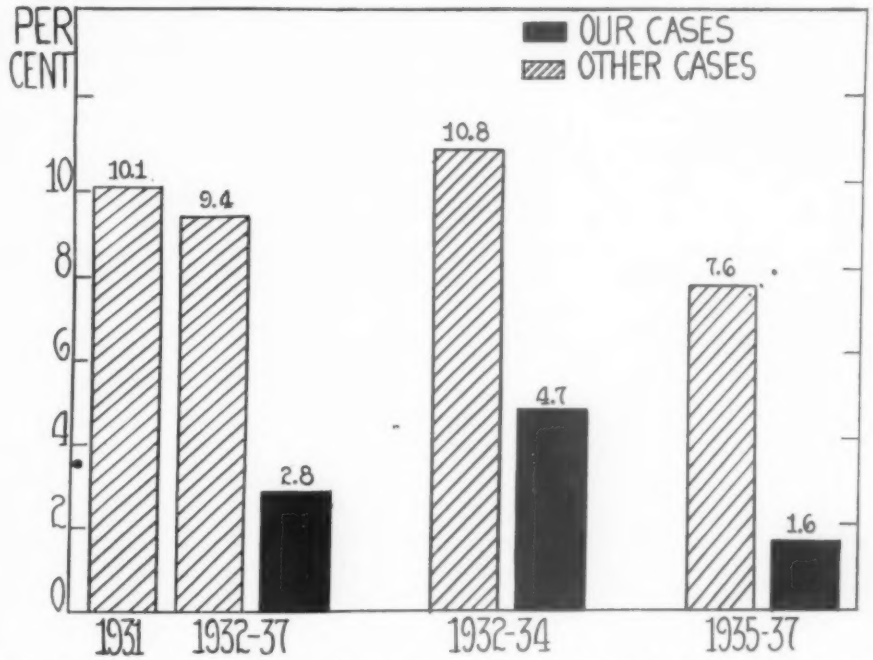


FIG. 1. Comparison of surgical mortality rates in patients with toxic goiter under our care, and those not under our care.

per cent for the rest of the hospital at the beginning of the study in order to give a better idea of the reduction that it has been possible to bring about. It is to be noted that in the last three years there has been some reduction in mortality among the patients we have not had charge of. This may be attributed in some degree to a change of attitude in the hospital as a whole toward the management of goiter, and to elimination of the severe reactions from fluid used parenterally. There is no doubt in our minds that the mortality for the hospital as a whole can be reduced to less than 2 per cent with careful supervision. In order to bring this about, however, the management of all patients with goiter should be turned over to a small group of individuals who are specially qualified to carry this out. The policy of letting many surgeons get a very limited experience in operating on patients with toxic goiter, together with the policy of keeping hospital beds free for use by quick turn-over of these patients on the medical wards, will inevitably maintain a high mortality rate.

It is also of interest to consider the mortality following operations for non-toxic goiter, which was largely of the adenomatous type. During the period 1932–37 there were 8 deaths in 290 patients not under our care—a mortality of 2.8 per cent: whereas during the period 1932–37 there was 1 death in 88 patients under our care—a mortality of 1.1 per cent. We do not have a sufficiently large number of cases to divide into two periods. During the period 1932–34 there were 7 deaths in 164 patients of other observers (4.3 per cent): whereas during 1935–37 there was 1 death in 126 patients (0.8 per cent). An important factor in the high rate during the first period was 4 deaths among their 69 patients in 1934 (5.8 per cent), a fact which is probably a coincidence, because during the same year they had their lowest mortality rate for toxic goiter.

Causes of Death

It is instructive to review the causes of death in our patients with toxic goiter. A brief analysis of them is given in table 3. Eight of the nine patients who died had exophthalmic goiter and one, toxic adenoma. Only two of the nine patients died of a crisis. In one (Mr. F. D.), death occurred seven hours after an unusually long operation involving much trauma. We did not consider the patient to be in very good condition for surgery at the time (1934) and at present would not permit operative procedures in a similar case. The other postoperative crisis developed in a thin, apathetic man (Mr. S. L.) in whom exophthalmic goiter was complicated by diabetes mellitus. He appeared, however, to be doing fairly well three to four days after operation, only to become worse in association with the development of pneumonia, from which he died five days after operation.

Three patients died from pneumonia. One (Mr. J. K), had a chill at midnight and a temperature of 100.2° F. at 5 a.m. the morning of operation. These signs were unfortunately not detected by the intern and the patient had been in good condition when we saw him the night before. Another man (Mr. C. P.) had had an upper respiratory infection which had supposedly cleared up by the time of operation, but after a careful review of his case, it is questionable whether he was completely well. In the third patient (Mrs. F. B.) there appeared to be no doubt that a fulminating bronchopneumonia was caused by unauthorized intratracheal anesthesia, which a resident in the nose and throat department was trying out, for removal of a substernal toxic adenoma. The tube was left in several hours after the operation and the patient died about 25 hours afterward.

One man 60 years old (Mr. A. N.) who suffered from arteriosclerotic heart disease and had previously been in the hospital with cardiac decompensation, was convalescing satisfactorily until he suddenly became unconscious 10 days after operation and died three hours later, probably from either a cerebral or coronary accident.

It is noteworthy that three patients died from sudden respiratory difficulty within 30 hours of operation. In two (Mr. C. F. and Mrs. M. C.),

TABLE III

Analysis of Deaths Following Thyroidectomy for Toxic Goiter, in Our Series

Patient	Age Yrs.	Diagnosis	Basal Metabolic Rate Per cent normal				Thyroidectomy	Length of Time Death Occurred After Operation	Cause of Death
			On Admission	Level During Rest	During Administration of Iodine				
					Lowest Level	Level Before Operation			
Mr. C. P.	53	Exophthalmic goiter Arteriosclerosis	+57	+54	+26	+33	Subtotal 11/10/33	2½ days	Bronchopneumonia. (Upper respiratory infection apparently not entirely cleared up at time of operation.)
Mr. S. L.	52	Exophthalmic goiter Diabetes mellitus	+49	+51	+27	+30	Subtotal 12/15/33	5 days	Thyroid crisis and pneumonia.
Mr. A. N.	60	Exophthalmic goiter Arteriosclerosis Chron. myocarditis Emphysema	+37	+20	+ 1	+21	Subtotal 3/ 5/34	10 days	Cerebral or coronary accident. (Suddenly became unconscious and died 3 hours later.)
Mr. F. D.	40	Exophthalmic goiter	+60	+38	+40	+55	Left hemi-thyroidectomy 3/13/34	7 hours	Thyroid crisis.
Mrs. L. T.	31	Exophthalmic goiter	+54	+41	—	—	Subtotal 3/17/34	13 hours	Pressure of hematoma on collapsible trachea.
Mr. C. F.	41	Exophthalmic goiter	+39	+46	+32	+32	Subtotal 11/10/34	4½ hours	Sudden respiratory difficulty. Probably bilateral cord paralysis.
Mrs. M. C.	47	Exophthalmic goiter	+65	+42	+14	+14	Subtotal 3/23/36	24 hours	Sudden respiratory difficulty from bilateral cord paralysis produced at operation.
Mrs. F. B.	51	Toxic adenoma (substernal)	+25		+20	+20	Subtotal 5/ 2/36	25 hours	Bronchopneumonia. (Unauthorized intratracheal anesthesia.)
Mr. J. K.	56	Exophthalmic goiter Cirrhosis of liver	+36	+18	− 1	− 1	Subtotal 8/20/26	4 days	Bronchopneumonia. (Temperature 100.2° F. at 5 a.m. morning of operation.)

this was apparently associated with bilateral paralysis of the vocal cords, and in one (Mrs. L. T.) was apparently caused by pressure from a hematoma on a collapsible trachea.

In retrospect, it would appear that the deaths in eight of these nine patients might have been prevented. The development of pneumonia in two patients might have been avoided by more careful search for an upper respiratory infection before operation, and in the third patient, we think would not have occurred if intratracheal anesthesia had not been used. The rather sudden death in the 60 year old man, ten days after operation, can scarcely be attributed to the operation itself, and probably would have occurred without it. The two crises might have been avoided by withholding surgery until the patients were in still better condition for operation. The three deaths from sudden respiratory difficulty were the result of purely surgical complications and could have been prevented by having adequate facilities for immediate passage of a life-saving tube, followed by tracheotomy. It is desirable that every patient have a special nurse for 48 hours following a thyroidectomy, so that emergencies may be detected as soon as they arise.

The single death among our patients with non-toxic goiter occurred in a woman of 37 with a large substernal goiter. A pack was not inserted as ordered by the surgeon and she developed a large hematoma in which an infection developed, leading to cellulitis of the neck, mediastinitis, bronchopneumonia, gangrene of the lung and finally death 23 days after operation. This again was a purely surgical complication.

We think it is significant that since 1934 not a single patient with toxic goiter of whom we have had charge has died of a postoperative crisis. This would appear to be largely the result of the great care used in preparing these patients for operation.

Factors Influencing Operative Mortality

Operative mortality is determined by (*a*) the condition of the patient, and (*b*) the skill of the surgeon.

General Preoperative Management

In previous communications we have discussed in some detail the various factors concerned in getting the patient into the best possible condition for operation.[1, 2, 3] These may be summarized as follows:

1. *The Administration of Iodine.* Within very wide limits the size of the dose and the form in which it is administered are not important.[2, 4] No longer do we necessarily follow the old dictum of carrying out operation from 10 to 14 days after starting iodine. All other factors known to be important in determining the outcome must be taken into consideration.

2. *Rest.* It is very important that this be properly regulated. In order to preserve muscle tone and prevent patients from becoming bedridden, rest

must not be complete except in the presence of cardiac decompensation or a thyroid crisis, and then only until the emergency has passed.

3. *A Diet Sufficiently High in Calories to Produce a Gain in Weight.* For most patients this means the administration of 4000 to 5000 calories a day. The regular high caloric diets of most hospitals are not adequate

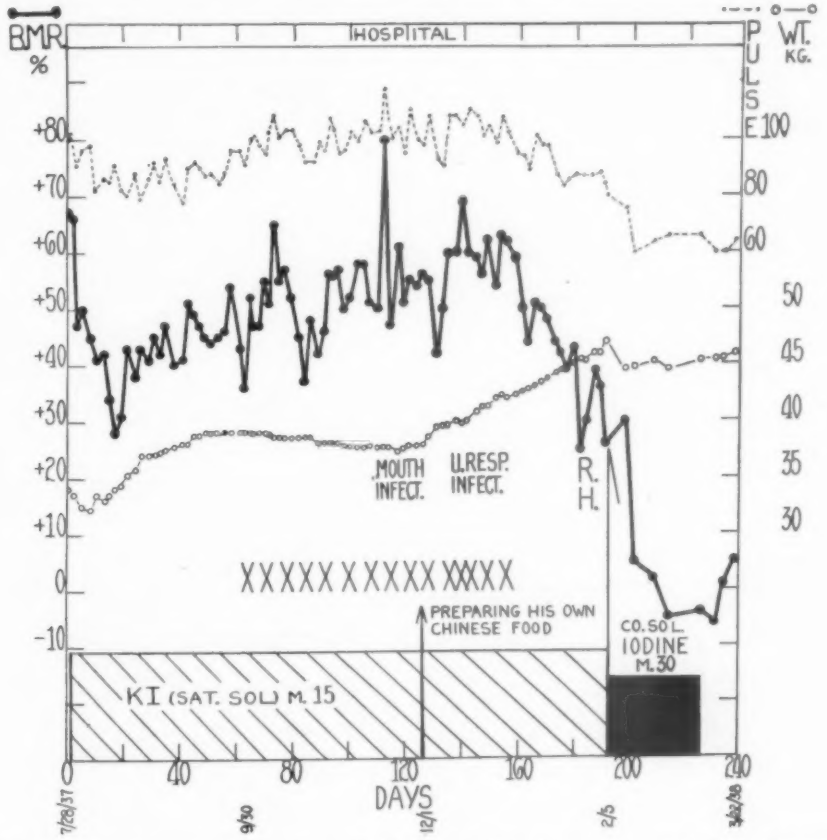


FIG. 2. Management of severe exophthalmic goiter in a very emaciated Chinaman. (H. B. T. Ht. 161 cm. Age 40 yrs.) Although there was at first a marked initial reduction in basal metabolism during the administration of iodine, he weighed only 34 kg. Note effect of catering to his dietary habits, and of using roentgen-ray therapy (X). Throughout the whole period preceding final gain in weight he was too weak to stand operative procedures. At time of operation (right hemithyroidectomy) he was in good condition and had only a moderate postoperative reaction.

for this purpose because they contain only about 3200 calories. It is usually unwise to operate unless weight is gained. Sometimes attention to details of dietary habits may be a life-saving measure. This is illustrated by a Chinaman (figure 2) who spoke English poorly and disliked our food. He weighed only 71 pounds and it was impossible to produce a sufficient increase in his weight until we let him get his own supply of rice and cook it to his taste in our laboratory.

4. *Roentgen-Ray Treatment in Patients with High Metabolic Rates, Refractory to Iodine.*

5. *The Administration of Digitalis in Cardiac Decompensation.*

Favorable signs in predicting the outcome of operation are: (1) Gain in weight, (2) Reduction in emotional instability and increase in muscle strength, (3) Reduction in basal metabolism during the administration of iodine, (4) Absence of upper respiratory infections, and (5) Absence of cardiac decompensation. With a well marked gain in weight there occurs a reduction in emotional instability and an increase in muscle strength, whether the basal metabolism drops or not.

It is usually safe to perform a thyroidectomy when:

1. The basal metabolism has dropped to plus 40 per cent or lower during the administration of iodine and the patient has gained 10 pounds or more in weight.
2. Emotional instability and muscle weakness are slight or when both have decreased markedly in association with a gain in weight of 10 pounds or more, even though the basal metabolism has dropped very little.
3. Cardiac decompensation, present on admission to the hospital, has completely disappeared, provided other factors are favorable. When edema is present on admission, loss of weight as a result of its disappearance must be taken into consideration in gauging the real change in the patient's weight.

It is ideal when, at the same time, the basal metabolism drops to within nearly normal limits, the weight increases and emotional instability and muscle weakness decrease markedly. However, such an ideal combination of favorable signs is encountered in only a small percentage of the patients.

In our experience it is usually unwise to operate when:

1. The patient fails to gain or is losing weight.
2. Emotional instability and muscle weakness are marked.[5]
3. The basal metabolism is plus 60 per cent or higher, in spite of the administration of iodine.
4. The disease is increasing rapidly in severity.[6]
5. Less than two weeks has elapsed after an upper respiratory infection has cleared up.
6. Cardiac decompensation is present.

A thyroidectomy is never an emergency procedure and when done as such often results in the death of the patient. The single most important principle is never to carry out surgical procedures until the condition of the patient has improved sufficiently to warrant them. The death of a patient is almost never caused by taking an adequate length of time for preoperative preparation. An example of the length of time occasionally necessary to prepare patients is illustrated in figure 2.

Management of Patients Refractory to Treatment

While we have developed certain general rules to aid us in deciding when a patient will or will not withstand surgical procedures, the decision in an individual case is not always easy. In an attempt to cover all possible contingencies we prefer to err on the side of conservatism. We can always delay an operation, but once a crisis has set in usually nothing will stop it. A certain proportion of patients are very difficult to prepare for operation for one reason or another, the failure commonly being associated with little or no reduction or even with a rise in metabolism during the administration of iodine. Sometimes in spite of a reduction in metabolism, patients fail to gain weight and continue to have marked muscle weakness and emotional instability. It is necessary to devise some method of preparing these poor risk patients for surgery. We have used roentgen-ray treatment, giving commonly one treatment at weekly intervals for a total of about twelve treatments. Because of some increase in the severity of the disease following each treatment, it is unwise to give them at shorter intervals. An example of what may be accomplished by roentgen-ray therapy is illustrated in figure 3.

By paying great attention to preoperative preparation, multiple stage operations can usually be avoided. However, whenever there is any doubt about how extensive surgical procedures the patient will tolerate, it is wise to do the operation in at least two stages. In rare instances we have resorted to ligations to test the ability of the patient to withstand surgery, although we doubt whether they have any other value.

Important Points in the Immediate Preoperative Preparation of the Patient

In addition to the more prolonged period of preparation for operation, it is important in the period immediately preceding operation:

1. To make a careful search for an upper respiratory infection or a sudden increase in the severity of the disease just before the patient goes to the operating room.
2. To administer a carbohydrate meal from six to eight hours before operation. This helps to prevent acidosis in the postoperative period and is more important than in persons with normal basal metabolism, because of the speed with which patients with toxic goiter burn food.
3. To administer the regular dose of iodine with this meal.
4. To institute, at least 24 hours before the scheduled time of operation, some program suitable for the control of emergencies in patients in whom the disease is complicated by diabetes.

Important Points in the Immediate Postoperative Treatment

In the immediate postoperative period the following points are important:

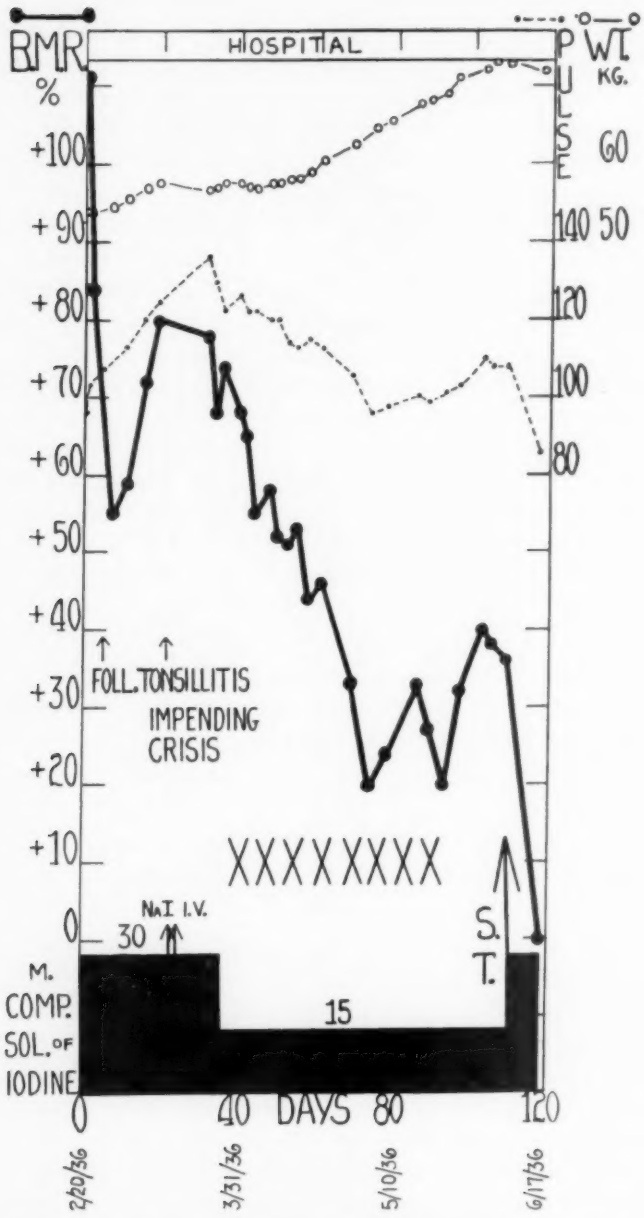


FIG. 3. The use of roentgen-ray treatment (X) in preparing a patient with severe, exophthalmic goiter for operation. (R. R. Ht. 160 cm. Age 30 yrs.) Note rapidity of rise in basal metabolism after initial reduction, in association with onset of an upper respiratory infection. Great severity of disease, in spite of iodine, precluded operation. After marked improvement with roentgen-ray therapy, subtotal thyroidectomy was performed with uneventful convalescence.

1. Careful observation of the wound for the early detection of excessive bleeding.

2. Careful observation of the patient to detect respiratory difficulty as soon as it arises, either from laryngeal or tracheal obstruction. Usually a paralysis of one vocal cord does not produce serious respiratory difficulty, but in its presence an emergency must be considered to exist until proved otherwise.

3. The services of a specially trained nurse for the first 48 hours, to report trouble as soon as it arises.

4. Facilities on the ward or in the patient's room for emergency passage of a life-saving tube and performance of a tracheotomy.

5. Intravenous administration of a suitable combination of salt and dextrose for prolonged or excessive vomiting, a thyroid crisis or circulatory collapse. When a thyroid crisis is present the continuous intravenous administration of fluid for several days may be a life-saving measure, circulatory collapse sometimes setting in shortly after it is stopped. If patients are properly prepared, most of them do not require the administration of fluid postoperatively by the parenteral route.

6. Administration of iodine to control any residual thyrotoxicosis.

7. Search for parathyroid tetany on the second to the fourth postoperative day, and its control with suitable measures, if observed.

Condition of Patient vs. Skill of Surgeon

The relative importance of the condition of the patient and the skill of the surgeon in the reduction of operative mortality is not easy to determine. As previously pointed out, it was largely by improving preoperative and postoperative management that we were able to reduce the rate from 10.8 per cent to 4.7 per cent. With still further improvement in these two factors and considerable selection of surgeons, we were able to reduce the rate further to 1.6 per cent. During the period 1932–37 three of the best surgeons had 5 deaths in performing 222 thyroidectomies for Thompson and Taylor—a mortality of 2.3 per cent; whereas they had 22 deaths in performing 297 thyroidectomies for other medical men—a mortality of 7.4 per cent. That surgical skill is important is obvious from the records of individual surgeons. Numerous examples of unnecessary complications developing after operation by unskillful men could be cited.

Comment

It has been demonstrated that even in a large, crowded, public hospital, where medical care is of the type available on a restricted budget and where the patients are largely from the poorest classes of society and commonly have the disease in its more advanced stages, it is possible to establish a mortality rate from operations for toxic goiter that approaches that obtained

in the best highly specialized thyroid clinics in this country. The medical care, although necessarily not of the quality most desirable, can, if constantly watched, be adequate in all essential elements; and the undernourishment so often noted in the patients can be overcome by special attention to their diet.

If hospitals wish to keep their mortality rates from thyroid surgery at the lowest possible figure, they must be willing to relegate the management of the patients to a group of internists and surgeons who are specially qualified in this field. What has been done in thyroid disease can be done in many other fields, notably that of gall bladder surgery. In all conditions involving surgical procedures, the outcome is determined by the preoperative condition and postoperative care of the patient, and the skill of the surgeon. These factors are not peculiar to thyroid surgery.

Summary

In a large public hospital it has been possible to reduce the mortality rate from operation for all cases of toxic goiter from 10.8 per cent to 1.6 per cent, and for exophthalmic goiter from 13.1 per cent to 1.5 per cent, by paying great attention to the preoperative and postoperative care of the patient and by restricting surgery for the most part to specially qualified men.

The most important factors in causing this reduction appear to have been care in improving the preoperative condition of the patient and postponement of operative procedures until it appeared highly probable that the patient could stand them.

A thyroidectomy is never an emergency procedure and when done as such commonly results in the death of the patient.

A crisis in the postoperative period usually means that the preoperative care has been inadequate.

It is usually unwise to operate when:

1. The patient fails to gain or is losing weight.
2. Emotional instability and muscular weakness are marked.
3. The basal metabolic rate is plus 60 per cent or higher, in spite of iodine.
4. The disease is increasing rapidly in severity.
5. Less than two weeks has elapsed after the disappearance of an upper respiratory infection.
6. Cardiac decompensation is present.

Roentgen-ray therapy is sometimes of value in preparing for operation patients who are refractory to other methods of treatment.

In retrospect, it seems probable that nearly all of the deaths in our series might have been prevented. Of nine patients with toxic goiter who died, in only two was the death the result of crisis, and in them the preoperative

condition was poor. In three it was caused by sudden respiratory difficulty, representing a purely surgical complication: in three by pneumonia: and one old man with heart disease died rather suddenly ten days after operation. Deaths from sudden respiratory difficulty can almost always be prevented by having adequate facilities available for immediate relief of the obstruction. The presence of upper respiratory infections must be watched for with the greatest care before operation, because they are an important cause of postoperative pneumonia.

If hospitals wish to keep their mortality rates at the lowest possible level, they must relegate the management of thyroid disease to internists and surgeons who are specially qualified in this field.

BIBLIOGRAPHY

1. Thompson, W. O., Taylor, S. G. III, and Meyer, K. A.: Factors influencing operative mortality in exophthalmic goiter, Ann. Int. Med., 1934, viii, 350.
2. Thompson, W. O.: Factors of importance in the treatment of exophthalmic goiter, Illinois Med. Jr., 1932, lxii, 520.
3. Thompson, W. O., Taylor, S. G. III, and Meyer, K. A.: The relation between the preoperative condition of the patient and operative mortality in exophthalmic goiter, Illinois Med. Jr., 1935, lxvii, 53.
4. Thompson, W. O., Thompson, P. K., and Cohen, A. C.: The range of effective iodine dosage in exophthalmic goiter. IV. The effect on basal metabolism of the daily administration of about 0.75 mg. of iodine, Arch. Int. Med., 1932, xlix, 199.
5. Mayo, C. H., and Plummer, H. S.: The thyroid gland, 1926, C. V. Mosby Company, St. Louis.
6. Mallory, T. B., Means, J. H., and Young, E. L.: Exophthalmic goiter and acute rheumatic fever, case no. 15472, New England Jr. Med., 1929, cci, 1056.

TREATMENT OF UNDULANT FEVER; A REPORT OF FIVE CASES TREATED WITH A SPECIFIC POLYVALENT SERUM *

By HARRISON F. FLIPPIN, M.D., *Philadelphia, Pennsylvania*

THE incidence of undulant fever in the United States is steadily on the increase. The United States Public Health Service statistics [1] for 1927 show only 112 cases as compared to 2008 reported in 1935. With this increase in the prevalence of the disease we find numerous reports [2] dealing with therapy. It is not the purpose of this paper to attempt to evaluate the various forms of treatment but to report five cases of the disease which were effectively treated with a specific polyvalent serum.†

The antimelitensis serum used in the treatment of these cases was a sterile polyvalent antiserum of bovine origin with preservative. Two separate groups of cattle were used in the production of the antiserum. One group received, intravenously, ascending doses of heat killed suspensions of *Brucella abortus.* The other group received in the same manner, heat skilled suspensions of *Brucella melitensis.* The cattle received doses of the antigen on three days of each week. The series of injections necessary to produce an agglutinin titer of 1 to 1600 or more against the specific antigen required approximately two months of such treatment. Sera of individual bleedings from each group having sufficient potency, to which 0.35 per cent phenol had been added as a preservative, were pooled and allowed to age. Equal parts of *Brucella abortus* antisera and *Brucella melitensis* antisera were mixed and filtered. The final mixture had an agglutinin titer of 1 to 800 against both *Brucella abortus* and *Brucella melitensis.*

The treatment in these cases varied somewhat at first as to the route of administration and dosage as we were concerned with serum reactions whose severity was then undetermined. We now believe the method of choice is an initial intramuscular injection of 1 c.c. of serum as a test dose followed in 24 hours, if no reaction occurs, by six daily intravenous injections of 50 c.c. of serum. The serum is best given with 100 c.c. of physiological salt solution over a fifteen minute period.

CASE REPORTS

Case 1. G. S., white male, 37 years of age, was admitted May 28, 1935, to Dr. T. Grier Miller's private service, complaining of recurrent attacks of chills, fever and headaches of 13 months' duration. Physical examination was negative, except for a

* Received for publication October 25, 1937.

From the Hematology Section and the Medical Clinic of the Hospital of the University of Pennsylvania.

† Antimelitensis serum, Sharp and Dohme Lot No. 85872.

palpable spleen. There was a moderate leukopenia, negative blood culture, a positive blood agglutination reaction for *Brucella abortus* in a dilution of 1 to 6400, and a

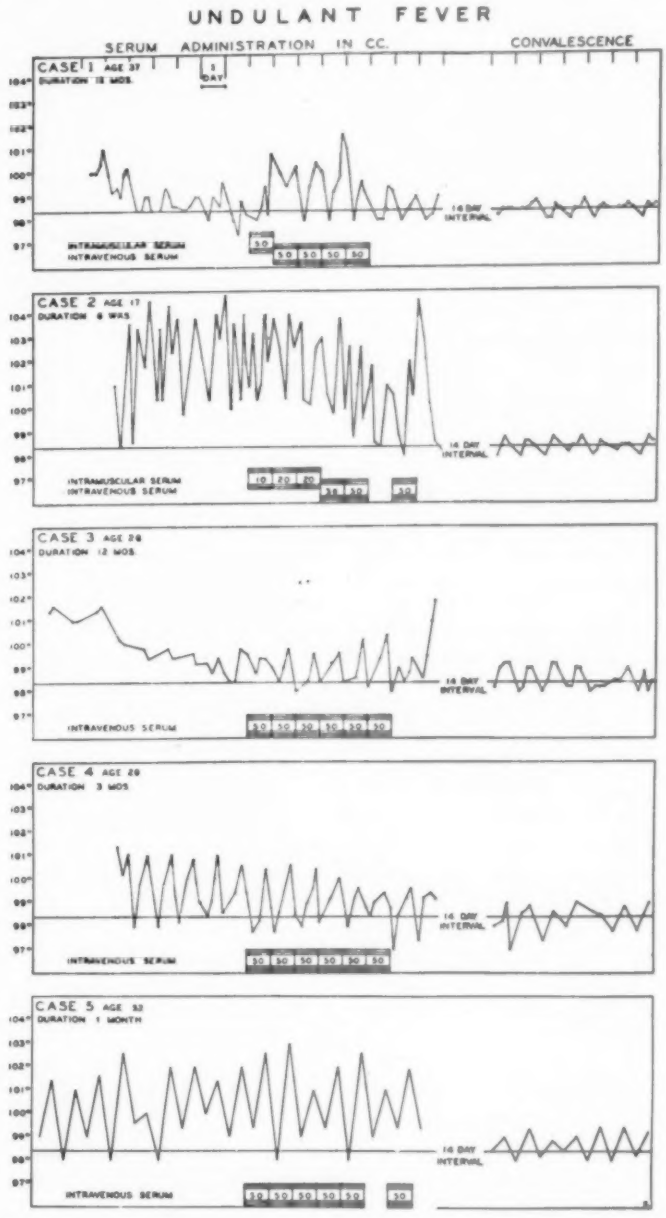


CHART 1. Showing temperature readings and serum administrations.

positive skin test for *Brucella abortus*. Chart 1 portrays the temperature readings and the time and amounts of serum administered as well as the mode of administration. There was a slight elevation of temperature and some itching of the skin fol-

lowing the first 50 c.c. of serum. The patient returned to work two weeks after the completion of this treatment and since then has remained in good health.

Case 2. L. W., white girl, 17 years of age, admitted July 31, 1935 to Dr. T. Grier Miller's private service, with a history of chills, sweats, and fever of four months' duration, during which time there were marked weight loss and weakness. A palpable spleen was the only positive physical finding. There was a moderate secondary anemia, slight leukopenia, negative blood culture, positive blood agglutination reaction for *Brucella abortus* in 1 to 2560 dilution, and a positive skin test for *Brucella abortus.* Temperature readings and serum administration are shown in chart 1. The only evidence of serum sickness was extreme weakness on the fifth day of treatment and for that reason serum was not given for 24 hours. The patient became symptom free within two weeks following the serum and has continued well.

Case 3. M. E., white female, 26 years of age, admitted September 27, 1936 to Dr. Thomas Fitz-Hugh's private service, complaining of weakness, loss of weight, sweats, and fever of 12 months' duration. Physical examination was negative. There was a moderate leukopenia, negative blood culture, positive blood agglutination for *Brucella abortus* in a dilution of 1 to 6400, and a positive skin test for *Brucella abortus.* The temperature readings and serum administration are shown in chart 1. There were no signs or symptoms of serum sickness. The patient became free of symptoms within three weeks after the completion of the serum therapy, and has remained in good health.

Case 4. J. C., white male, 29 years of age, admitted September 24, 1936 to Dr. Alfred Stengel's ward service, suffering with marked weakness, loss of weight, night sweats, chills and fever of three months' duration. Physical examination was negative except for evidence of weight loss and a palpable spleen. There was a moderate secondary anemia, slight leukopenia, negative blood and urine cultures, positive blood agglutination for *Brucella abortus* in a dilution of 1 to 5120, and a positive skin test for *Brucella abortus.* Temperature readings and serum administration are shown in chart 1. There was no evidence of serum sickness. The patient became free of symptoms within two weeks after receiving serum and has remained well.

Case 5. E. F., white male, 52 years of age, admitted November 12, 1936 to Dr. Alfred Stengel's private service, with a history of weight loss, profuse sweats, and fever of one month's duration. Physical examination was essentially negative. There was a moderate leukopenia, negative blood culture, a positive blood agglutination for *Brucella abortus* in 1 to 6400 dilution, and a positive skin test for *Brucella abortus.* Temperature readings and serum administration are shown in chart 1. There was no appreciable serum reaction. Serum was not given on the sixth day due to a misunderstanding. Except for weakness, the patient became essentially free from symptoms within three weeks after serum therapy. Since that time the patient has remained in good health.

Discussion

In this report we have included every case of undulant fever that was treated with serum in this hospital. The duration of illness in these cases was from 1 to 13 months. Aside from the usual routine measures, none of these patients received any other form of therapy than the specific polyvalent serum. The diagnosis was made in all cases by a typical history, a positive skin test, and a positive blood agglutination in high titers for *Brucella abortus.* At this time all five cases are in good health, with apparent cures ranging in duration from 8 to 24 months. We have made no attempt to explain the mechanism of recovery. Whether the beneficial ef-

fects are due to the specific action of the serum or not, is beyond the purpose of this report. We are merely presenting five proved cases of undulant fever which apparently recovered, following the administration of a specific polyvalent serum.

We wish to express our appreciation to Dr. L. J. Wenger of the Sharp and Dohme laboratories for his help in this study.

BIBLIOGRAPHY

1. Personal communication from the Division of Sanitary Reports and Statistics, United States Public Health Service.
2. Carpenter, C. M., and Boak, R. A.: The treatment of human brucellosis: a review of current therapeutic methods, Medicine, 1936, xv, 103–127.

DETERMINATION OF THE NORMAL CIRCULATION TIME FROM THE ANTECUBITAL VEINS TO THE PULMONARY CAPILLARIES BY A NEW TECHNIC *

By SAMUEL CANDEL, M.D., *Brooklyn, New York*

IN the original determinations on the velocity of blood flow in man by Blumgart and Weiss,[1] a method was employed in which radium was injected. This required an elaborate apparatus for the detection of radium and did not lend itself to wide clinical use, so that in later studies, simpler methods were devised.

The vast majority of the tests now practiced have for their starting point the injection of some substance into a vein in the antecubital fossa. The time that it takes that substance to move in the blood stream to another fixed point is measured. Depending upon the method used, the circulation time through one or the other of two pathways is determined. One ends in the pulmonary capillaries and includes the venous channels from the antecubital fossa through the superior vena cava to the right auricle, the right ventricle and the pulmonary artery. The other ends in capillaries which are the terminal branches of a systemic arteriole and includes the venous channels leading from the antecubital fossa through the superior vena cava to the right auricle, the right ventricle, the pulmonary artery, the pulmonary capillaries, the pulmonary vein, the left auricle, the left ventricle and the aorta.

The measurement of the first pathway includes only the right heart and gives us what is known as the "pulmonary circulation time." The measurement of the second circuit is spoken of as the "complete circulation time" and includes both the right heart and the left heart. In this paper we shall deal only with a method for measuring the pulmonary circulation time.

The methods which are now commonly employed to measure the pulmonary circulation time consist in the injection into one of the antecubital veins of a volatile substance such as ether,[2, 3] perfumes, guaiacol, sodium cacodylate, allyl sulphide, methyl salicylate,[3] colloidal sulphur.[4] The time it takes for the appearance of their characteristic odors on the breath is measured. The test may be used either subjectively by instructing the patient to signal immediately on perceiving the odor, or objectively, by the observer himself smelling the drug.

The methods which have been just described have the following disadvantages:

* Received for publication July 24, 1937.
From the Medical Service of Dr. M. A. Rabinowitz.

1. If the patient is required to notify the operator when he perceives the odor, then the method shares the disadvantages common to all subjective methods.

2. If the operator relies upon his own sense of smell, the method still has the disadvantage that the sense of smell in man is the most poorly developed of all his faculties.

Several years ago, Dr. Charles H. Birnberg [5] of the Department of Obstetrics, in attempting to produce amnesia during labor by the intravenous administration of paraldehyde, noticed that practically all patients would cough before the needle was removed from the vein. When this observation was described to the present investigator, the possibility occurred to him of making this the basis of a new method for the determination of the pulmonary circulation time.

A perusal of the literature revealed that Noel and Souttar [6] were apparently the first to use paraldehyde intravenously as a hypnotic. They observed that in five seconds the patient tasted paraldehyde. In ten seconds the patient had a sensation of dizziness. It is significant that the authors used paraldehyde and found it a safe hypnotic even in grave cardiac and pulmonary disease.

Honan and Hassler [7] administered a mixture of ether and paraldehyde intravenously for anesthesia. They reported excellent results but discontinued their use because the drugs were rapidly eliminated from the lungs and seemed to produce a decided irritation of the larynx.

Collier [8] used a mixture of paraldehyde and ether intravenously as an anesthetic, and in four cases observed that paraldehyde appeared on the breath 30, 10, 15, and 10 seconds, respectively, after the injection.

Nitzescu and Iacobovici [9] utilized paraldehyde in an isotonic solution of glucose for basal anesthesia. They reported 82 cases with satisfactory results aside from the disagreeable odor on the breath.

Johnson [10] gave 5 c.c. of paraldehyde intravenously. The patient lost consciousness in 10 seconds and coincidently with the onset of anesthesia, the patient coughed and a strong smell of paraldehyde was noted on the breath. He found the drug satisfactory because it was stable, easy to procure, required no sterilization and had a wide margin of safety.

Beauchemin et al.[11] induced general anesthesia in 55 patients. Their average dose was 9.2 c.c. for an adult weighing 60 kilograms. Nineteen cubic centimeters, the largest dose used, was given to an individual weighing only 46 kilograms. They noticed that a cough occurred during the injection and discussed a method of administration devised to decrease the cough.

Since paraldehyde is excreted in the lungs and produces a cough, can readily be procured, requires no sterilization, and since relatively large amounts can be injected without harmful effect, we did not hesitate to apply

its intravenous injection in order to develop an objective method * for the determination of the pulmonary circulation time.

I have found that 1.4 c.c. (an amount about one-sixth as large as the average therapeutic dose for anesthesia) is the minimum volume of paraldehyde which when given intravenously produces a cough reflex most consistently. In some individuals, 0.8 c.c. and in one patient, 0.2 c.c. was sufficient. Therefore, in practically every case, 1.4 c.c. of paraldehyde (U.S.P.) was the dose used. The time which elapsed between the moment of injection and the appearance of the cough was measured with a stopwatch.

One hundred males and females, with apparently normal cardio-vascular systems, varying in age from 15 to 70 years were tested by this method. The results of these tests are summarized in table 1. The injections were given through a large bore needle (18 gauge) so that no time would be lost on account of mechanical resistance to the introduction of the drug.

TABLE I

* Blood Velocity in 100 Patients with Apparently Normal Cardiovascular Systems

AGES OF PATIENTS	Pulmonary Circulation Time in Seconds *				TOTALS
	3–4.5	5–6.5	7–8.5	9 or more	
61 years and over	1	3	3	0	7
46–60 years	3	11	4	3	21
31–45 years	6	19	4	3	32
15–30 years	3	25	9	3	40
TOTALS	13	58	20	9	100

* Corrected to nearest half second.

A cough reflex was obtained in 96 per cent of the cases where 1.4 c.c. of paraldehyde was used. The cough paroxysm lasted from a few seconds to 2 or 3 minutes. Two of the patients fell asleep for a few minutes, after the injection of the drug. When they awoke they had no unpleasant aftereffects. Most of the other patients complained of a sensation of dizziness, but this wore off quickly. Another complication, which occurred in three cases, was venous thrombosis. However, there was no sloughing of tissue or other harmful result.

As has just been mentioned, no cough reflex was produced in four instances. In these, however, when the test was repeated after 15 minutes,

* It may be mentioned that the test may be modified and used as a subjective one, utilizing a smaller dose of paraldehyde. The end point would then be given by the patient signalling in some way that he has smelled the drug.

a cough reflex was obtained. In such cases, or where too small amounts are injected to produce a cough reflex, one can use as an end-point, a sudden marked change in facial expression when the patient begins to smell the obnoxious substance.

Since the possibility existed that the circulation time had some correlation with the age of the patient, the results of the present study are classified according to the age of the patient (table 1). However, the various groups in table 1 are too small in numbers to permit the calculation of any correlation which might or might not exist. Therefore, the table has been condensed into 9 groups of patients to form table 2 and the distribution of the various circulation times was calculated for each age group.

TABLE II

Relation between Age of Patient and Pulmonary Circulation Time

Ages of Patients		Pulmonary Circulation Time in Seconds			Totals
		3–4.5	5–6.5	7–10.5	
46 years or over	No. cases....	4	14	10	28
	Per cent.....	0.14±.04*	0.50±.06	0.36±.06	100
31–45 years	No. cases....	6	19	7	32
	Per cent.....	0.19±.05	0.59±.05	0.22±.05	100
15–30 years	No. cases....	3	25	12	40
	Per cent.....	0.07±.03	0.63±.05	0.30±.05	100
	Total.....	13	58	29	100
	Per cent.....	0.13±.02	0.58±.03	0.29±.02	100

* In this paper, the figure following the ± sign denotes the probable error. The probable error $= \pm 0.6745\sqrt{\frac{P(1-P)}{N}}$

P = frequency in per cent.
N = Total number of cases.

In addition to the frequency, the probable error of each frequency was calculated. It is apparent almost on inspection that there is no significant difference in the circulation time in different age groups. For example, let us take an apparently extreme difference, namely, between the frequency of occurrence of a short circulation time (column 1) in the age groups, 15 to 30 years and 31 to 45 years. In the former group, the frequency is 7 per cent and in the latter 19 per cent, so that the difference between the two frequencies is 12 per cent.

The probable error of a difference $= \sqrt{P_1^2 + P_2^2}$ where P_1 and P_2 are the probable errors of the two observed frequencies, which are being compared, provided that the observed frequencies are independent of one another, as in the present instance. Hence, the probable error of the difference in question $= \sqrt{(.05)^2 + (.03)^2} = \sqrt{.0034} = .06$ or 6 per cent. Hence,

even this apparently extreme difference (12 per cent) is less than 3 times its probable error. From this we may conclude that there is no correlation between age and circulation time.

Since there is no correlation between age and the pulmonary circulation time, it is permissible to combine all the observations when calculating the normal range (table 3).

TABLE III

Calculation of Mean and Standard Deviation

P.C.T.*	f	x	fx	x^2	fx^2
3.0	3	−3.0	− 9.0	9.0	27.0
3.5	2	−2.5	− 5.0	6.25	12.50
4.0	4	−2.0	− 8.0	4.0	16.0
4.5	4	−1.5	− 6.0	2.25	9.0
5.0	24	−1.0	−24.0	1.0	24.0
5.5	10	−0.5	− 5.0	0.25	2.5
Arbitrary Mean 6.0	19	0.0	0.0	0.0	0.0
6.5	5	+0.5	+ 2.5	0.25	1.25
7.0	11	+1.0	+11.0	1.0	11.0
7.5	2	+1.5	+ 3.0	2.25	4.5
8.0	5	+2.0	+10.0	4.0	20.0
8.5	2	+2.5	+ 5.0	6.25	12.5
9.0	4	+3.0	+12.0	9.0	36.0
9.5	0	+3.5	+ 0.0	12.25	0.0
10.0	4	+4.0	+16.0	16.00	64.0
10.5	1	+4.5	+ 4.5	20.25	20.25
TOTALS	100		+ 7.0		260.5

* Pulmonary circulation time corrected to nearest half second.
f = absolute frequency of occurrence.
x = deviation from the arbitrary mean.

$$\text{Arbitrary Mean} = 6.0$$

$$\text{True Mean} = \text{Arbitrary Mean} + \frac{\Sigma fx}{\Sigma f}$$

$$= 6 + \frac{7}{100}$$

$$= 6.07 \text{ seconds}$$

$$\text{Standard Deviation} = \sqrt{\frac{\Sigma fx^2}{\Sigma f} - \delta^2}$$

$$= \sqrt{\frac{260.5}{100} - (0.07)^2}$$

$$= 1.61$$

(δ = Difference between arbitrary and true means)

Thus, it may be seen that the mean pulmonary circulation time, by the author's method, is 6.07 seconds and the standard deviation about the mean

is 1.61 seconds. The probable error of the mean

$$= \pm 0.6745 \frac{\text{Standard Deviation}}{\sqrt{N}},$$

where N = number of patients tested

$$= \pm 0.6745 \frac{1.61}{\sqrt{100}}$$

$$= \pm 0.11 \text{ seconds}$$

The probable error of the standard deviation

$$= \pm 0.6745 \frac{\text{Standard Deviation}}{\sqrt{2N}}$$

$$= \pm 0.08$$

Summarizing, Mean = 6.07 ± 0.11 seconds

Standard Deviation = 1.61 ± 0.08 seconds

Since 95 per cent of all random observations will fall between the limits of 2 times the standard deviation added to and subtracted from the mean, we may take the normal range as 2.8 to 9.3 seconds. When a determination falls outside of this range the odds against its being normal are 20 to 1. Since 99.7 per cent of the normal observations will fall within the range, mean $\pm$ 3 times the standard deviation, if a pulmonary circulation time greater than 11 seconds is encountered, the odds are approximately 300 to 1 that the finding is abnormal.

Discussion

The average pulmonary circulation time as determined by Hitzig [2] was 4 to 8 seconds. The average time obtained by Miller [3] was 6 to 9 seconds though there were occasional determinations as low as 3.5 seconds and others as high as 11.5 seconds.

In our series, the calculated mean was approximately 6 seconds. The normal range may be taken as about 3 to 9.5 seconds. A finding over 11.0 seconds can safely be considered abnormal since the odds are 300 to 1 against its being normal.

The method of determining circulation time by using paraldehyde has the following advantages:

(1) The end point, a sharp cough, is purely objective.

(2) The drug has a wide margin of safety.

(3) The drug is readily available and may be taken directly from the bottle without previous preparation or sterilization.

The disadvantages of the use of paraldehyde are:

(1) It causes a transitory dizziness which, however, passes away in several minutes.

(2) Rarely, in the doses used, it may cause complete hypnosis lasting a few minutes. However, there were no unpleasant after-effects when the patient recovered from the hypnosis.

(3) The cough usually lasts from 1 to 3 minutes. It may be paroxysmal and hard. Theoretically, it might seem unwise to produce a cough paroxysm in a cardiac patient for whom the test would most frequently be indicated. Actually, in a series of such patients, now being studied, the cough has resulted in no untoward symptoms.

(4) Venous thrombosis may occasionally result, but the frequency of this complication is much lower than with other drugs that have been used.

Conclusions

1. A new method for the determination of the pulmonary circulation time is described.

2. 1.4 c.c. of paraldehyde, intravenously, was the dose used.

3. A cough reflex was obtained in 96 per cent of cases at the first attempt. In the other 4 per cent, a cough was produced upon repeating the test.

4. There is no correlation between the age groups studied and the pulmonary circulation time.

5. The mean value of the pulmonary circulation time in 100 adult male and female patients with apparently normal cardio-vascular systems was approximately 6 seconds. The normal limits are 3 and 9.5 seconds.

6. A finding of a pulmonary circulation time over 11.0 seconds is almost certainly abnormal.

I wish to express my deep gratitude to Dr. Meyer A. Rabinowitz for his inspiration and constant encouragement which has always marked the relationship of the master to his pupils.

I am greatly indebted to Dr. A. S. Wiener of the Department of Genetics and Biometrics of the Jewish Hospital for his invaluable aid in the statistical analysis.

I also wish to thank the services of Dr. Louria and Dr. Sussman from which some of the cases used in the present study were taken.

BIBLIOGRAPHY

1. Blumgart, H. L., and Weiss, S.: Studies on velocity of blood flow; method of collecting the active deposit of radium and its preparation for intravenous injection, Jr. Clin. Invest., 1927, iv, 389–398.
2. Hitzig, W. M.: Measurement of the circulation time from the antecubital veins to the pulmonary capillaries, Proc. Soc. Exper. Biol. and Med., 1934, 935–938.
3. Miller, H. R.: Velocity of blood flow in part of the pulmonary circulation, Proc. Soc. Exper. Biol. and Med., 1934, xxxi, 942–944.
4. Michalover, S.: Personal Communication.
5. Birnberg, C. H.: Personal Communication.
6. Noel, H., and Souttar, H. S.: The anesthetic effects of the intravenous injection of paraldehyde, Ann. Surg., 1913, lvii, 64–67; Lancet, 1912, 818.
7. Honan, W. F., and Hassler, J. W.: Intravenous anesthesia, Ann. Surg., 1913, lviii, 900–926.

8. Collier, G. K.: Intravenous use of paraldehyde, New York State Jr. Med., 1914, xiv, 130.
9. Nitzescu, I. I., and Iacobovici, I.: Nouveau procédé d'anesthésie générale; anesthésie de base par injection intraveineuse de paraldéhyde glucosée, Presse Med., 1934, xlii, 331–333.
10. Johnson, A. S.: The parenteral administration of paraldehyde for the control of pain and convulsive states, New England Jr. Med., 1934, xxi, 1065–1067.
11. Beauchemin, J. A., Springer, R. G., and Elliott, G. A.: Intravenous anesthesia, Med. Times and Long Island Med. Jr., 1935, lxiii, 179–184.

THE VALUE OF SULFANILAMIDE IN THE TREATMENT OF INFECTIONS OF BLADDER AND UPPER URINARY TRACT; REPORT OF STUDY OF TWENTY-FIVE PATIENTS *

By William J. Ezickson, A.B., M.D., *Philadelphia, Pennsylvania*

Following the epochal work of Domagk,[1] wherein he used with success the original Prontosil, in the treatment of streptococcic infections, many investigators abroad reported their findings with the use of this drug. Scherber,[2] Anselm,[3] Kramer,[4] and others reported excellent results from its administration in clinical cases of puerperal fever, erysipelas, etc. Following this Colebrook and Kenny [5] proved its value in the treatment of puerperal infection due to hemolytic streptococci. The first American report was made by Long and Bliss,[6] in which they corroborated experimentally and clinically the work done abroad. All this earlier work showing the value of the original prontosil and of sulfanilamide in the treatment of infection due to streptococcus has been corroborated and greatly extended since.

The value of sulfanilamide in the treatment of infections other than those due to the streptococcus was early reported. Buttle, Gray and Stevenson,[7] and Proom [8] showed its usefulness in meningococcic infections; Cooper, Gross and Mellon,[9] and Rosenthal [10] in type III pneumococcic infections and Dees and Colston,[11] in gonococcic infections.

After very careful study the Council on Pharmacy and Chemistry of the American Medical Association [13] voted to accept sulfanilamide for inclusion in New and Non-Official Remedies as a therapeutic agent for the treatment of infections by hemolytic streptococci of Lancefield's serologic group A (May 29, 1937).

Clinical Investigation

A group of 25 patients, having various types of infections of the bladder and upper urinary tract, were studied and treated with sulfanilamide. This group included for the most part, patients who have been under our care for a period of several months to several years, for infections of kidney and bladder, and who failed to respond to any previous treatment.

This study included the following data: (1) Age; (2) Sex; (3) Previous history; (4) Present diagnosis; (5) Symptoms before treatment; (6) Duration of symptoms; (7) Appearance of urine before treatment; (8) Culture of urine before treatment; (9) Total number of days treated; (10) Improvement noted (number of days after treatment was instituted); (11) Symptoms after treatment; (12) Appearance of urine after treatment;

* Received for publication November 27, 1937.

From the Calculus Research and Urologic Clinics, Department of Urology, Pennsylvania Hospital, Philadelphia, Pa.

(13) Culture of urine after treatment; (14) Average pH of urine during treatment; (15) Reaction; (16) Present condition.

The accompanying table briefly summarizes these data (table 1).

Age. The age groups were as follows:

Between 20 and 30	1
" 30 and 40	5
" 40 and 50	9
" 50 and 60	6
" 60 and 70	1
over 70	3

Sex. Twenty-one males and four females were studied and treated.

Previous History. One patient (case 3) had a left nephrectomy in 1927 for renal tuberculosis and also a bilateral epididymectomy (tuberculosis) in 1929. Four patients (cases 7, 8, 11 and 15) had urethral strictures, one of which (case 15) was complicated with a perineal fistula and an external perineal urethrotomy was done. Six patients (cases 6, 9, 12, 14, 24 and 25) had a transurethral prostatic resection. The length of time elapsing from the time of operation until present treatment was from three weeks to three years. Seven patients (cases 1, 16, 17, 18, 19, 20 and 21) had renal or ureteral calculi or both, with renal or bladder infection. Three of these had a ureterolithotomy; one had a pyelolithotomy; one a nephrolithotomy; one had a nephrectomy and one had two pyelolithotomies and a nephrectomy. Two patients (cases 2 and 4) had several attacks of pyelonephritis over a period of several years. Two patients (cases 5 and 10) had symptoms of prostatism with chronic myocarditis and arteriosclerosis. One patient (case 22) had a perineal prostatectomy. One patient (case 13) had a suprapubic prostatectomy in 1935; a transurethral resection of contracted vesicourethral orifice in 1936 and this was followed by incontinence of urine, which condition still exists. One patient (case 23) had chronic prostatitis and cystitis.

Present Diagnosis.—Cystitis: Nine patients (cases 4, 6, 9, 12, 13, 14, 22, 24 and 25).

Pyelonephritis: Four patients (cases 16, 17, 19, 21).

Urethral stricture and cystitis: Three patients (cases 7, 11, 15).

Prostatic hypertrophy with cystitis: Two patients (cases 5 and 10).

Prostatitis and cystitis: Two patients (cases 8 and 23).

Calculus pyonephrosis and cystitis: Two patients (cases 1 and 18).

Pyelonephritis and cystitis: Two patients (cases 2 and 20).

Renal and bladder tuberculosis with mixed infection: One patient (case 3).

Symptoms before Treatment. Most of the patients (18 cases) had the following symptoms: Frequency, diurnal and nocturnal, urgency and dysuria. Several in this group also had hematuria. The others (7 cases) had lumbar pain and some dysuria.

Duration of Symptoms. This varied from several months to five years. Ten of these patients had symptoms from one to two years; nine from two to five years and only six under one year.

Appearance of Urine before Treatment. The urine before treatment was cloudy in all but two instances, and in these it was hazy.

Cultures of Urine before Treatment. The *B. coli* was found in the cultures of the urine before treatment in eleven of the cases. In two instances culture revealed *B. pyocyaneus* and *B. coli;* in two cases, Friedlander's bacillus; in one case *Staphylococcus albus;* in one case *Staphylococcus albus hemolyticus* and non-hemolytic streptococcus; in one case, a pure culture of hemolytic streptococci; in one case *Staphylococcus albus hemolyticus* and hemolytic streptococci; in one case non-hemolytic *Staphylococcus albus;* in one case an unidentified gram positive micrococcus; in one case there was no growth in 72 hours.

Total Number of Days Treated. Treatment was carried out for from one to eleven weeks. Most of the patients (14 cases) were not treated for more than four weeks. Only two were continued on treatment for more than eight weeks.

Improvement Noted. (Number of days after treatment was instituted.) Sixteen patients showed improvement, symptomatic or clearing of the urine or both, within one week. Two showed improvement in 10 days; two in two weeks; one in three weeks and four showed no improvement at any time. Two of the 16 patients who showed improvement within one week continued this improvement for a period of about four to six weeks and then all the original symptoms returned in as severe a form as before treatment was started.

Symptoms after Treatment. Most of the patients (18 cases) had the following symptoms before treatment: frequency, urgency, dysuria and nocturia. In every instance but three, these symptoms disappeared entirely or were diminished in severity after from one to two weeks' treatment. The most persistent symptom was nocturia but in most instances the number of voidings at night was much decreased.

Appearance of Urine after Treatment. The urine became clear in 15 cases. The appearance improved from cloudy to hazy in six cases and there was no improvement in the cloudiness of urine in four cases.

Culture of Urine after Treatment. In nine cases a negative culture of the urine was obtained after one to four weeks of treatment. The organisms found in this group before treatment were chiefly the *B. coli* and the streptococcus. In the remaining 16 cases a wide variety of results were obtained. In two patients who had both renal and bladder infection (*B. coli*) a negative culture was obtained from the involved kidney but the *B. coli* was still found in the bladder urine. No change occurred in the cases in which we had found the *B. proteus,* Friedlander's bacillus or the *B. pyocyaneus,* before treatment. In several of the cases in which we obtained

Case No.	Name	Sex	Age	Previous History	Diagnosis	Symptoms Before Treatment	Duration of Symptoms	Appearance of Urine Before Treatment	Culture Before Tr
1.	G.I.	M.	46	Ureterotomy (R) 5/28/32 Calculus pyonephrosis (L)	Calculus pyonephrosis (L)—Cystitis	Frequency-nocturia 3–4—hematuria	5 years	Cloudy	Friedlander's
2.	G.V.	M.	37	Infection (L) kidney 1935	Pyelonephritis—bilateral —cystitis and prostatitis	Plain left renal area Frequency and urgency Nocturia 2x–3x	1½ years	Cloudy	*B. coli* from b and bladder
3.	A.A.	M.	38	Nephrectomy (L) for renal T.B. 1927 Bilateral epididymectomy for T.B. 1929	Renal and bladder tuberculosis	Marked frequency and urgency, nocturia 10–12, dysuria, hematuria	3 years	Much debris, bloody, cloudy	*B. Pyocyaneus* *B. Coli*
4.	H.W.	M.	40	1922-Gall bladder operation May 1932—Herniorrhaphy Several attacks pyelonephritis	Cystitis	Constant right renal pain, dysuria, some frequency	5 years	Cloudy	Culture both k ative. Cultu —non-hemol tococcus
5.	R.A.	M.	60	Chronic myocarditis Arteriosclerosis	Prostatic hypertrophy Grade 1. Cystitis	Frequency, urgency, dysuria, nocturia 4x–5x	3 years	Cloudy	6/3/37—*B. fe ligenes* 6/29/37—scant *Staphylococcu* (Hemolytic), growth—hem
6.	D.G.	M.	55	Encrusted cystitis—median lobe Prostatic enlargement—Transurethral resection—Dec. 1935	Cystitis	Dysuria, frequency, urgency, nocturia 10–12	4 years	Cloudy	B. of colon gro
7.	J.M.	M.	52	Apr. 1929—Intestinal obstruction Laparotomy—July 1934—torsion of Meckel's diverticulum; resection diverticulum Jan. 1937—Incisional hernia	Urethral stricture Cystitis	Frequency, nocturia 4x–5x Dysuria, urgency	2 years	Cloudy	B. of colon gro
8.	J.A.	M.	47	Peri-urethral abscess Urethral stricture—syphilis	Cystitis and prostatitis	Frequency, urgency, nocturia 2–3, dysuria, L.L.Q. pain	9 months	Cloudy	Atypical *B. coli*
9.	J.B.	M.	54	Transurethral prostatic resection—April 1934	Cystitis	Frequency, urgency, dysuria, nocturia 2x–3x	3 months	Cloudy	6/21/37—*B. coli*
10.	L.G.	M.	74	Cataracts—bilateral general arteriosclerosis Symptoms of prostatism	Median lobe enlargement Cystitis (marked)	Frequency, dysuria, urgency, nocturia 6x–7x Residual 3 oz.	1½ years	Very cloudy	Unidentified bac Unidentified mic (gram positive)
11.	E.L.	M.	52	Urethral stricture—2 operations—lues	Urethral stricture Marked cystitis	Frequency, urgency, dysuria, small stream Bilateral renal pain	8 months	Cloudy	No growth 72 h
12.	A.B.	M.	46	Fracture pelvis and right leg Feb. 1937—prostatic resection June 11, 1937	Cystitis	Frequency, dysuria, nocturia 4x–5x	4 months	Very cloudy and bloody	*B. coli*
13.	G.D.	M.	68	Prostatectomy 1935—contracture vesico-urethral orifice Feb. 1936—prostatic resection—contracture vesico-urethral orifice—April 1936—resection followed by incontinence	Cystitis	Incontinence—nocturia 4x	16 months	Cloudy	*B. proteus*
14.	S.DA.	M.	53	Prostatic hypertrophy—median lobe—transurethral prostatic resection—June 1937	Cystitis	Dysuria	6 months	Cloudy	*B. pyocyaneus* *B. coli*
15.	D.B.	M.	47	1933—Stricture urethra with perineal fistula 1934—ischio-rectal abscess 1936—external perineal urethrotomy	Urethral stricture Perineal fistula Cystitis	Frequency, urgency, nocturia 1x	2½ years	Cloudy and blood tinged	*B. coli* and P group
16.	R.DA.	F.	50	1925—Pyelolithotomy (R) 1933—Pyelolithotomy (R) 1936—Nephrectomy (L)	Pyelonephritis (right kidney) calculus Cystitis	Some frequency and nocturia 1x	2 years	Cloudy	*B. coli* (R. kidney
17.	C.L.	F.	38	Hysterectomy 1932 Rt. nephrolithotomy Oct. 1936	Pyelonephritis-right	Dysuria at times	3 years	Hazy	R. kidney—*B. co* Bladder—*B. coli*
18.	M.U.	F.	47	Appendectomy and supra vaginal hysterectomy 1934—April 1936 developed hematuria. Stag-horn calculi left kidney also fair sized calculus right kidney Pyelolithotomy (R) May 28, 1937	Pyonephrosis (left) Calculus	Bilateral renal pains G. I. Symptoms	1½ years	Cloudy	R. kidney—*Staph albus* non-hemol L. kidney—*Staph albus* non-hemol Bladder—*Staphyl albus*
19.	J.G.	M.	27	Rt. ureteral calculus—Oct. 1936 Ureterolithotomy—Oct. 1936	Pyelonephritis (R)	Occasional right renal pain, frequency, dysuria	1 year	Cloudy	5/28/37—Pure cul molytic streptoc
20.	A.K.	F.	32	Ureteral calculus 1929—passed spontaneously. 1933—calculus left kidney with pyonephrosis. Dec. 1936—uretero-lithotomy lt.	Pyelonephritis (L) Cystitis	Slight distress over operative area	4 years	Cloudy	Friedlander's bacil
21.	A.S.	M.	41	Stag-horn calculus left-kidney. Nephrectomy 8/6/36. History of renal calculi for 4 years previous	Pyelonephritis (right kidney)	Renal colic (R) 7/23/37 Hematuria, frequency, nocturia	3 months	Cloudy	*Staphylococcus albu*
22.	C.J.	M.	74	Phimosis 1937—Circumcision Perineal prostatectomy Apr. 1937	Cystitis	Frequency, dysuria, nocturia 8x–10x	1 year	Very cloudy, much debris	*B. proteus*
23.	W.G.	M.	36	Gonorrhea 1934—chronic prostatitis and cystitis 1935	Prostatitis Cystitis	Constant dull pain R.L.Q. slight mucopurulent discharge (urethral) in a.m.	1½ years	Hazy and shreds	Few *Staphylococcu* (hemolytic) Non-hemolytic str
24.	C.S.	M.	57	March 1937—Enlarged prostate with 1,000 c.c. residual cloudy urine—prostatic resection	Cystitis and epididymitis —bilateral	Frequency, urgency, nocturia 5x–6x	1½ years	Cloudy	*B. coli*
25.	J.S.	M.	73	Cardio-vascular disease with decompensation—June 1934 Prostatic resection—Sept. 1934	Arteriosclerosis Myocarditis	Frequency, nocturia (3x–4x)—some dysuria	3 years	Cloudy and debris	*B. coli*

Culture of Urine Before Treatment	Total No. Days Treated	Improvement Noted No. Days After Treatment Instituted	Symptoms After Treatment	Appearance Urine After Treatment	Culture of Urine After Treatment	pH	Reaction
llander's bacillus	8 weeks	Symptomatic improvement only	No urinary symptoms	Cloudy	Friedlander's bacillus	7.0–7.5	None
li from both kidneys l bladder	6 weeks	7 days	None	Clear	No growths after 48 hrs.	5.0–5.5	None
yocyaneus *oli*	8 weeks	7 days	All symptoms disappeared except nocturia 2x–3x for 6 weeks then symptoms returned	Slightly hazy, few shreds	6/4/37—Mixed growth *B. proteus* and B. of colon group. Few *B. pyocyaneus*, few unidentified cocci 7/3/37—*B. pyocyaneus* 7/22—B. of colon group	5.5–6.0	2 weeks after treatment developed acute gastro-enteritis (nausea, vomiting, diarrhea) subsided in 3 days
ure both kidneys negve. Culture bladder on-hemolytic streptoccus	6 weeks	7 days	None	Clear	6/24/37—Non-hemolytic streptococcus 8/25/37—Non-hemolytic strep. Few diphtheroids	5.0–6.5	Slight weakness first day
7—*B. fecalis alkaues* 37—scant growth *phylococcus albus* molytic), scant vth—hemolytic strep.	5 weeks	7 days	Slight dysuria Nocturia x1	Clear	No growths in 72 hrs.	5.5–6.5	Slight dizziness first day of treatment
colon group	11 weeks	7 days	All symptoms disappeared except nocturia 1x–2x	Hazy	7/7—Friedlander's bacillus 7/22—paracolon B. 8/19—*B. colon* group. Few Friedlander's	6.0–7.5	Slight dizziness and weakness in legs
colon group	10 weeks	7 days	None	Clear	7/15—scant growth diphtheroids 8/12—*Staphylococcus albus* diphtheroids	5.5–6.0	For first five days had marked weakness and dizziness
cal *B. coli*	5 weeks	7 days	None	Hazy and shreds	7/2—Mixed scant growth *Streptococcus viridans* and diphtheroids	6.0–6.5	Feeling of drowsiness and leg weakness for 2 days
37—*B. coli*	8 weeks	7 days	Slight dysuria	Clear	7/3—*B. proteus* 7/24—*B. proteus* 8/7—*B. proteus* 8/14—*B. proteus* 8/21—*B. proteus*	5.5–6.0	Dizzy and weak while taking medicine
ntified bacilli ntified micrococci m positive) (Staph.?)	3 weeks	7 days	All symptoms disappeared except nocturia 2x	Clear	7/8—*B. coli* and unidentified growth. Neg. cocci	6.0–7.0	First few days dizziness and leg weakness
owth 72 hours	2 weeks	7 days	None	Clear	No growths after 72 hrs.	5.5–6.0	None
i	2 weeks	7 days	None	Hazy	7/8—No growths after 48 hours	5.0–5.5	None
teus	3 weeks	None	Nocturia 3x–4x Incontinence	Cloudy	7/17—*B. proteus* 7/24—*B. proteus*	7.0–7.5	None
ocyaneus *i*	1 week	7 days	None	Clear	No growths in 48 hours	5.5–6.0	None
li and Para-colon p	4 weeks	None	None	Cloudy and bloody	*B. coli*	6.5–7.5	Slight dizziness first day
(R. kidney)	7 weeks	7 days	None	Hazy	6/24—R. kidney—no growth in 48 hours 6/24—Bladder—*B. coli* 7/28—*B. coli* 8/11—*B. coli*	5.5–6.0	None
lney—*B. coli* er—*B. coli*	4 weeks	7 days	None	Clear	7/21—R. kidney—No growth Bladder—*B. coli*	6.0–6.5	While taking medicine complained of peculiar tingling in fingers and toes, very nervous
ney—*Staphylococcus* non-hemolytic ney—*Staphylococcus* non-hemolytic er—*Staphylococcus*	6 weeks	3 weeks	None	Hazy	7/21—Scant growth—*Staphylococcus albus* (non-hemolytic) 8/5—*Staphylococcus albus* 8/19—Scant growth—large growth—positive cocci	5.0–5.5	Very weak and dizzy while taking medicine
7—Pure culture hetic streptococcus	5 weeks	2 weeks	None	Clear	7/22—*Staphylococcus albus*—hemolytic 8/11—no growth 48 hours	5.0–6.0	Had severe reaction first few days. Dizzy, fever, weakness. Drug cut down to 2 a day. No react.
ander's bacillus	3 weeks	None	None	Cloudy	7/28—Friedlander's bacillus	6.0–7.0	Dizzy and headache first 2 days. Medication discontinued
lococcus albus	2 weeks	10 days	None	Clear	8/18—Gram-positive bacilli	6.0–6.5	None
teus	3 weeks	7 days	None	Clear	7/24—*B. proteus*—non-hemolytic strep. 8/7—*B. proteus*	6.0–7.0	Slight dizziness first day of treatment
Staphylococcus albus olytic) emolytic strep.	4 weeks	12 days	None at end of 12 days	Clear	7/28—scant growth *Staphylococcus albus* (non-hemolytic) 8/12—no growth	5.5–6.5	None
	4 weeks	10 days	None—epididymitis—markedly improved	Clear	8/14—*Streptococcus viridans* 8/19—unidentified micrococci 8/24—hemolytic strep. 9/2—no growth in 48 hours	5.0–5.5	None
	1 week	7 days	All disappeared except nocturia 1x	Clear	8/19—no growth in 48 hours	5.0–6.0	None

Diagnosis	Symptoms Before Treatment	Duration of Symptoms	Appearance of Urine Before Treatment	Culture of Urine Before Treatment	Total No. Days Treated	Improvement Noted No. Days After Treatment Instituted	Symp Tr
pyonephrosis stitis	Frequency-nocturia 3–4—hematuria	5 years	Cloudy	Friedlander's bacillus	8 weeks	Symptomatic improvement only	No urinary
phritis—bilateral s and prostatitis	Plain left renal area Frequency and urgency Nocturia 2x–3x	1½ years	Cloudy	*B. coli* from both kidneys and bladder	6 weeks	7 days	None
nd bladder tu- sis	Marked frequency and urgency, nocturia 10–12, dysuria, hematuria	3 years	Much debris, bloody, cloudy	*B. Pyocyaneus* *B. Coli*	8 weeks	7 days	All sympto except r for 6 wee toma retu
	Constant right renal pain, dysuria, some frequency	5 years	Cloudy	Culture both kidneys negative. Culture bladder —non-hemolytic streptococcus	6 weeks	7 days	None
hypertrophy Cystitis	Frequency, urgency, dysuria, nocturia 4x–5x	3 years	Cloudy	6/3/37—*B. fecalis alkaligenes* 6/29/37—scant growth *Staphylococcus albus* (Hemolytic), scant growth—hemolytic strep.	5 weeks	7 days	Slight dysu Nocturia x
	Dysuria, frequency, urgency, nocturia 10–12	4 years	Cloudy	B. of colon group	11 weeks	7 days	All symptor except noc
stricture	Frequency, nocturia 4x–5x Dysuria, urgency	2 years	Cloudy	B. of colon group	10 weeks	7 days	None
nd prostatitis	Frequency, urgency, nocturia 2–3, dysuria, L.L.Q. pain	9 months	Cloudy	Atypical *B. coli*	5 weeks	7 days	None
	Frequency, urgency, dysuria, nocturia 2x–3x	3 months	Cloudy	6/21/37—*B. coli*	8 weeks	7 days	Slight dysur
obe enlargement (marked)	Frequency, dysuria, urgency, nocturia 6x–7x Residual 3 oz.	1½ years	Very cloudy	Unidentified bacilli Unidentified micrococci (gram positive) (Staph.?)	3 weeks	7 days	All symptom except noct
stricture cystitis	Frequency, urgency, dysuria, small stream Bilateral renal pain	8 months	Cloudy	No growth 72 hours	2 weeks	7 days	None
	Frequency, dysuria, nocturia 4x–5x	4 months	Very cloudy and bloody	*B. coli*	2 weeks	7 days	None
	Incontinence—nocturia 4x	16 months	Cloudy	*B. proteus*	3 weeks	None	Nocturia 3x– Incontinence
	Dysuria	6 months	Cloudy	*B. pyocyaneus* *B. coli*	1 week	7 days	None
stricture fistula	Frequency, urgency, nocturia 1x	2½ years	Cloudy and blood tinged	*B. coli* and Para-colon group	4 weeks	None	None
phritis (right kid- loulus	Some frequency and nocturia 1x	2 years	Cloudy	*B. coli* (R. kidney)	7 weeks	7 days	None
phritis-right	Dysuria at times	3 years	Hazy	R. kidney—*B. coli* Bladder—*B. coli*	4 weeks	7 days	None
rosis (left) s	Bilateral renal pains G. I. Symptoms	1½ years	Cloudy	R. kidney—*Staphylococcus albus* non-hemolytic L. kidney—*Staphylococcus albus* non-hemolytic Bladder—*Staphylococcus albus*	6 weeks	3 weeks	None
phritis (R)	Occasional right renal pain, frequency, dysuria	1 year	Cloudy	5/28/37—Pure culture hemolytic streptococcus	5 weeks	2 weeks	None
phritis (L)	Slight distress over operative area	4 years	Cloudy	Friedlander's bacillus	3 weeks	None	None
phritis (right kid-	Renal colic (R) 7/23/37 Hematuria, frequency, nocturia	3 months	Cloudy	*Staphylococcus albus*	2 weeks	10 days	None
	Frequency, dysuria, nocturia 8x–10x	1 year	Very cloudy, much debris	*B. proteus*	3 weeks	7 days	None
itis	Constant dull pain R.L.Q. slight mucopurulent discharge (urethral) in a.m.	1½ years	Hazy and shreds	Few *Staphylococcus albus* (hemolytic) Non-hemolytic strep.	4 weeks	12 days	None at end of
and epididymitis teral	Frequency, urgency, nocturia 5x–6x	1½ years	Cloudy	*B. coli*	4 weeks	10 days	None—epididy markedly imp
sclerosis rditis	Frequency, nocturia (3x–4x)—some dysuria	3 years	Cloudy and debris	*B. coli*	1 week	7 days	All disappear nocturia 1x

Symptoms After Treatment	Appearance Urine After Treatment	Culture of Urine After Treatment	pH	Reaction	Present Condition
No urinary symptoms	Cloudy	Friedlander's bacillus	7.0–7.5	None	No urinary symptoms No clinical improvement
None	Clear	No growths after 48 hrs.	5.0–5.5	None	Well
All symptoms disappeared except nocturia 2x–3x for 6 weeks then symptoms returned	Slightly hazy, few shreds	6/4/37—Mixed growth *B. proteus* and B. of colon group. Few *B. pyocyaneus*, few unidentified cocci 7/3/37—*B. pyocyaneus* 7/22—B. of colon group	5.5–6.0	2 weeks after treatment developed acute gastro-enteritis (nausea, vomiting, diarrhea) subsided in 3 days	Marked improvement for 6 weeks, then all previous symptoms returned
None	Clear	6/24/37—Non-hemolytic streptococcus 8/25/37—Non-hemolytic strep. Few diphtheroids	5.0–6.5	Slight weakness first day	Entirely well symptomatically
Slight dysuria Nocturia x1	Clear	No growths in 72 hrs.	5.5–6.5	Slight dizziness first day of treatment	Marked improvement
All symptoms disappeared except nocturia 1x–2x	Hazy	7/7—Friedlander's bacillus 7/22—paracolon B. 8/19—*B. colon* group. Few Friedlander's	6.0–7.5	Slight dizziness and weakness in legs	Slight improvement
None	Clear	7/15—scant growth diphtheroids 8/12—*Staphylococcus albus* diphtheroids	5.5–6.0	For first five days had marked weakness and dizziness	Well
None	Hazy and shreds	7/2—Mixed scant growth *Streptococcus viridans* and diphtheroids	6.0–6.5	Feeling of drowsiness and leg weakness for 2 days	Marked improvement
Slight dysuria	Clear	7/3—*B. proteus* 7/24—*B. proteus* 8/7—*B. proteus* 8/14—*B. proteus* 8/21—*B. proteus*	5.5–6.0	Dizzy and weak while taking medicine	Marked improvement
All symptoms disappeared except nocturia 2x	Clear	7/8—*B. coli* and unidentified growth. Neg. cocci	6.0–7.0	First few days dizziness and leg weakness	Marked improvement for 4 weeks then all symptoms recurred
None	Clear	No growths after 72 hrs.	5.5–6.0	None	Entirely well. No urinary symptoms
None	Hazy	7/8—No growths after 48 hours	5.0–5.5	None	Marked improvement
Nocturia 3x–4x Incontinence	Cloudy	7/17—*B. proteus* 7/24—*B. proteus*	7.0–7.5	None	No improvement
None	Clear	No growths in 48 hours	5.5–6.0	None	Entirely well
None	Cloudy and bloody	*B. coli*	6.5–7.5	Slight dizziness first day	No improvement
None	Hazy	6/24—R. kidney—no growth in 48 hours 6/24—Bladder—*B. coli* 7/28—*B. coli* 8/11—*B. coli*	5.5–6.0	None	Marked improvement
None	Clear	7/21—R. kidney—No growth Bladder—*B. coli*	6.0–6.5	While taking medicine complained of peculiar tingling in fingers and toes, very nervous	Marked improvement
None	Hazy	7/21—Scant growth—*Staphylococcus albus* (non-hemolytic) 8/5—*Staphylococcus albus* 8/19—Scant growth—large growth—positive cocci	5.0–5.5	Very weak and dizzy while taking medicine	Somewhat improved
None	Clear	7/22—*Staphylococcus albus*—hemolytic 8/11—no growth 48 hours	5.0–6.0	Had severe reaction first few days. Dizzy, fever, weakness. Drug cut down to 2 a day. No react.	Well
None	Cloudy	7/28—Friedlander's bacillus	6.0–7.0	Dizzy and headache first 2 days. Medication discontinued	No improvement
None	Clear	8/18—Gram-positive bacilli	6.0–6.5	None	Marked improvement
None	Clear	7/24—*B. proteus*—non-hemolytic strep. 8/7—*B. proteus*	6.0–7.0	Slight dizziness first day of treatment	Marked improvement
None at end of 12 days	Clear	7/28—scant growth *Staphylococcus albus* (non-hemolytic) 8/12—no growth	5.5–6.5	None	Entirely well
None—epididymitis—markedly improved	Clear	8/14—*Streptococcus viridans* 8/19—unidentified micrococci 8/24—hemolytic strep. 9/2—no growth in 48 hours	5.0–5.5	None	Entirely well
disappeared except Nocturia 1x	Clear	8/19—no growth in 48 hours	5.0–6.0	None	Entirely well

a culture of *B. coli* before treatment we found that the *B. coli* had disappeared but found other organisms: *B. proteus,* diphtheroids, Friedlander's bacillus and *Streptococcus viridans.*

pH of the Urine. The pH of the urine in these patients varied from 5.0 to 7.5. The pH of most of most of them (18 cases) was found to be from 5.0 to 6.5.

Reactions. No reaction occurred in 11 cases. Twelve patients complained of some of the following symptoms during the first few days of medication: dizziness, weakness in the legs, tingling sensation in the fingers and toes. One of these developed a temperature of 101° for 24 hours, which subsided when medication was stopped and did not recur when it was started again. One patient developed a very acute attack of gastroenteritis with nausea, vomiting, diarrhea and fever. All these symptoms disappeared within 48 hours after medication was discontinued. In one case the dizziness and headache were so marked after the first few doses that medication had to be stopped immediately and we have been unable to give this patient any of the drug, even a 5 grain dose, without a reaction. Therefore no further treatment was attempted with this drug in this case.

Present Condition. Nine cases (36 per cent) are entirely well. Eight cases (32 per cent) showed marked improvement. Two showed marked improvement for several weeks and then had recurrence of all previous symptoms. Two showed slight improvement. Four showed no improvement. Therefore 68 per cent of this group are either entirely well or show marked improvement.

Dosage. Eighty grains of sulfanilamide were given each patient the first day and 40 grains per day for the next six days. After the first week the dosage varied from 20 to 30 grains per day. If reaction occurred, the drug was immediately discontinued for one to two days. On continuing the drug the dosage was started at 15 grains per day and gradually increased until 30 or 40 grains per day were taken. In several instances the drug could not be tolerated if more than 10 to 15 grains per day were taken.

Summary

A careful study of the value of sulfanilamide in the treatment of 25 patients with infections of the bladder or upper urinary tract or both, showed the following:

1. Most of the patients had infections of long duration (1 to 5 years) which had not responded to the various, usual methods of treatment.
2. Many varieties of organisms were found on culture of kidney and bladder urine before treatment was started.
3. Most of the patients (16 cases) showed symptomatic improvement, or clearing of the urine within one week.
4. Before treatment the urine was cloudy in every case but two (in which it was hazy), and after treatment the urine became clear in 15 cases and hazy in 6 cases. Only four cases showed no improvement.

5. The best results were obtained in those cases where we found the *B. coli* and the streptococcus. We obtained no improvement in those cases where the *B. proteus,* Friedlander's bacillus or *B. pyocyaneus* were found.

6. No serious reactions occurred.

7. Since, in the final analysis, 17 of these patients (68 per cent) are now entirely well or show marked improvement, we believe that sulfanilamide is a very valuable drug in the treatment of infections of the bladder and upper urinary tract.

However, in view of the widespread and promiscuous use of this drug in infections of the genito-urinary tract, we wish to state most emphatically, that no patient should be given this drug before a complete urologic study has been carried out. This study may reveal a pathological condition which may require surgery or some other form of treatment and sulfanilamide in such instances may be valueless and prove harmful.

The indiscriminate use of this drug, without careful and complete preliminary studies, must be condemned.

REFERENCES

1. Domagk, G.: Ein Beitrag zur Chemotherapie der bakteriellen Infektionen, Deutsch. med. Wchnschr., 1935, lxi, 250.
2. Scherber, G.: Zur lokalen und allgemeinen Behandlung des Rotlauf, in letzterer Beziehung mit besonderer Darstellung der Anwendung des Farbstoffpräparates Prontosil (Streptozon Praparat 5214) wie der Behandlungsresultate mit Omnadin, Wien. med. Wchnschr., 1935, lxxxv, 284, 346, 376; Die Behandlung des Rotlauf mit interner Prontosiltherapie kombiniert mit intravenosen Omnadininjektionen, *ibid.,* 1935, lxxxv, 783; Zur Behandlung der verschiedenen Formen des Pemphigus chronicus mit Antileprol und Prontosil, *ibid.,* 1936, lxxxvi, 22.
3. Anselm, E.: Unsere Erfahrungen mit Prontosil bei Puerperalfieber, Deutsch. med. Wchnschr., 1935, lxi, 264.
4. Kramer, W.: Ueber Erfahrungen bei der Erysipelbehandlung mit Prontosil, München. med. Wchnschr., 1936, lxxxiii, 608.
5. Colebrook, L., and Kenny: Treatment of human puerperal infections and of experimental infections in mice, with prontosil, Lancet, 1936, i, 1279; Treatment with prontosil of puerperal infections due to hemolytic streptococci, *ibid.,* 1936, ii, 1319.
6. Long, P. H., and Bliss, E. A.: Para-amino-benzene-sulfonamide and its derivatives, Jr. Am. Med. Assoc., 1937, cviii, 32.
7. Buttle, G. A. H., Gray, W. H., and Stevenson, D.: Protection of mice against streptococcus and other infections by para-amino-benzene-sulfonamide and related substances, Lancet, 1936, i, 1286.
8. Proom, H.: Therapeutic action of para-amino-benzene-sulfonamide in meningococcal infection of mice, Lancet, 1937, i, 16.
9. Cooper, F. B., Gross, P., and Mellon, R. R.: Action of para-amino-benzene-sulfonamide on Type III pneumococcus infections in mice, Proc. Soc. Exper. Biol. and Med., 1937, xxxvi, 148.
10. Rosenthal, S. M.: Chemotherapy of experimental pneumococcus infections, Public Health Rep., 1937, lii, 48.
11. Dees, J. E., and Colston, J. A. C.: The use of sulfanilamide in gonococcic infections, Jr. Am. Med. Assoc., 1937, cviii, 1855–1858.
12. Report of Council on Pharmacy and Chemistry, Am. Med. Assoc.: Sulfanilamide and related compounds, Jr. Am. Med. Assoc., 1937, cviii, 1888–1890.

A BROADER VIEW OF POSTMORTEM EXAMINATIONS *

By Alan Gregg, *New York, N. Y.*

Mr. President and Gentlemen:

I shall not explore the limits of your patience or abuse the courtesy of your attention by proffering in twenty minutes' time the brief of a long debate or the essence of a book. Let me rather submit to you only three scattered experiences of the past few years and conclude with a question which you are better qualified to answer than any other persons I know. The experiences may seem unrelated at first but I trust a certain coherence will be evident in due course, and I hope eagerly for as many answers later from you individually as may be possible since a sound understanding of any question calls for many corrections and qualifications.

I belong to a dinner club that plans a series of meetings at which a representative of each of several professions will advise the rest of us how the services of his profession can best be used by the laity. An architect, for example, will tell the rest of us how we can best make use of an architect's knowledge and experience, how to protect ourselves against incompetence or selfishness, what the layman should know of the architect's professional ethics and usages, on what terms does the architect give his best services, where lie pitfalls of misunderstanding between him and his client, what course, in short, would be wisest for the client to pursue in order to put the architect in the easiest position to give his services most effectively. And similarly we shall call upon some of the other professions; for example, an investment counselor, a newspaperman, an insurance expert, a lawyer, and—a physician. For in a society so differentiated into special callings as is the society of our times we are all laymen in everything but our own professions. And I would hold it to be wise to learn whatever possible of how to approach and maintain effective relations with other professions than one's own, and to learn this at a time divorced if not remote from the pressure of immediate need. It is probably equally wise too for every profession to cultivate public understanding rather than merely to court general approval.

And so from this dinner club plan inevitably I had and indeed still have the general question before me: "What advice could be given to laymen on how best to utilize a doctor's services?" I have postponed an answer which deserves so much reflection. A number of other questions have emerged in the meantime. To restate the matter let us repeat the formula for the architect, but this time in terms of the physician: How can the layman best make use of the physician's knowledge and experience? How can he

* Read before the American College of Physicians, New York, N. Y., April 4, 1938.

protect himself against incompetence and selfishness? What should the layman know of the physician's professional ethics and usages? On what terms does the physician give his best services? Where lie pitfalls of misunderstanding between physician and patient? In short, what course would be wisest for the layman to pursue in order to get the most benefit from a physician? Mark you, how to choose a good doctor is not within this question; that is another story. It is how to get the best from him once the choice is made. Are there any steps the layman can take to ensure as well as encourage the best of medical performance—and has he ever been told them by someone unrelated to the occasion of their use?

The next experience has been spread over the past seven years—I have realized the extraordinary fluidity of the population of the United States in contrast to the stability of residence of the Europeans. Travel by automobile has not only replaced much travel by train but it has extended the number and range of trips, excursions, visits, and it has encouraged moving and changes of residence. We think nothing of distance. We are the most restless and movable people on earth—or above it. Consequently a seriously large number of persons, separately or in families, must call an unknown physician in some unfamiliar place of residence. Now this is done usually on a basis that scarcely deserves the words *choice* or *selection*. The situation lacks the reassurance of long acquaintance with our informants or advisors. It may be hurried and urgent. It may be incredibly haphazard. Doctors are often chosen under circumstances which make it more than ever important that mutual understanding attend their relationship to patients. And so it was my second experience to realize that in America especially, because of its constantly moving population, the layman needs a map of our ways. He needs to be told how we can best help him.

Lastly an experience of three years ago in the clinicopathological conference room of a well known medical school. I saw by chance a blackboard lying on its side in apparent neglect. On it were written the percentages for the preceding quarter of postmortem examinations secured on deaths (*a*) on the private wards and (*b*) on the public wards; 13 per cent of the private patients who died came to post mortem; 82 per cent of the patients on the public wards came to post mortem. Quite appropriately that table of figures on post mortems was lying on its side, for it bore evidence of neglect of one of the most enlightening and stimulating practices we physicians know—the postmortem examination. We know the post mortem can and does improve our efforts at diagnosis, we know it is the terror of the casual guesser, we know it is a reward to an eager and honest doctor even when it is a stark corrective, we know it increases our competence and knowledge—in sum, we know the post mortem serves as a merciless incentive to the best we have in us as physicians.

But does the layman know? Let me draw these three experiences together now in the question I wish to ask you: Shall the layman be told

this incentive to our best performance? Is it not true that if a layman wishes to get the best possible service from a physician he would be wise to say at the outset of an illness—"Now Doctor, there's one thing I should like to have clear: if worse comes to worst there is to be a post mortem"?

In increasing measure the American of all classes uses a hospital. *We* know that he would be wise to demand rather than reluctantly concede the performance of a postmortem examination. But does he know it? I doubt it. And is it wise for him and for us that he should remain any longer uninformed of a safeguard within his reach?

I have never heard the layman's interest mentioned in discussions of post mortems. The postmortem examination has been emphasized as a way to advance scientific knowledge, or it has been thought of as a generous concession to the forgivable curiosity of a beloved doctor, or it has been urged as a method without equal in maintaining staff efficiency in hospitals —but I would inquire whether anyone unprejudiced and remote from the event has ever shown the laity where its interests lie in the matter of post mortems? Is it reasonable to tell the layman that the warning of a post mortem might urge and convert an incompetent doctor in time from proud isolation to prudent consultation? Is it reasonable to say that the mention of a post mortem would never lessen the interest of a competent and trustworthy doctor? Is it reasonable to state quite candidly that in the request for post mortems the public has a means of protecting its own interests? To have an understanding with a physician that if death comes an autopsy will follow involves, as it seems to me, no extra risk whatever to the patient.

The question perhaps suggests that two assumptions are being taken for granted: one that there are no great objections in the lay mind to post mortems, and the other that there are enough competent pathologists ready for such a revolutionary change. Neither of these assumptions is true at present, but both are capable of becoming true gradually and at a rate that will not jeopardize the change. Both were even more valid objections when hospitals began to secure post mortems. If, as the phrase goes, "no effort is to be spared to improve the patient's chances" is it not time to have it widely known that experience shows that the practice of post mortems has improved the patient's chances?

There is real need for each profession to teach the laity how best to use its services. In America where with increasing frequency doctors' services are called in ignorance of their capacities, the ways of protecting the laity are of importance. Among other means too numerous to mention at this time one simple suggestion is then here offered for your comment: the performance of postmortem examinations, in that it has greatly improved our efforts as doctors, should be known by the laity as an advantage also within their power to demand.

So the essential point is this: do you endorse my view that one simple but powerful piece of advice in his own protection the layman could wisely

be given is this—" Explain to whomever you call that if death comes a post mortem will be required "? It may be grim advice—but in the cause of good medicine we do not shirk giving grim advice. It may not be heeded—we have had that experience too. But it can be understood—and because it is in the interest of the patient, the post mortem can change gradually from being hated and feared and avoided to being used and trusted and steadily perfected. We have known similar transitions in the past. Already, as many of you know, the clinicopathological conference is the wonder and admiration of many of our foreign visitors, who see in it a candor and fearlessness altogether to the credit of American medicine.

CASE REPORTS

BENZEDRINE AND PAREDRINE IN THE TREATMENT OF ORTHOSTATIC HYPOTENSION, WITH SUPPLEMENTARY CASE REPORT *

By Horace Marshall Korns, M.D., and William Lloyd Randall, M.D.,
Iowa City, Iowa

In January, 1937, in a report [1] of our experience with benzedrine in the treatment of orthostatic hypotension, we pointed out that if amounts of either benzedrine or ephedrine sufficiently large to maintain the blood pressure within normal limits were employed for more than a few days at a time, it became difficult, even with full doses of the various barbiturates, to overcome the consequent insomnia. When this statement caught the eye of Mr. W. F. Thompson, of the Smith, Kline and French Laboratories, he suggested that we try paredrine (beta-parahydroxyphenylisopropylamine), a related amine, which, according to preliminary pharmacologic studies,[2, 3, 4] has a greater pressor action than benzedrine and none of its stimulating effect on the central nervous system, and kindly offered to supply enough paredrine for the experiment.

The results which we obtained are summarized in the following table; the measurements are representative of a large series.

Table I

	Column 1	Column 2	Column 3	Column 4		Column 5	
	Untreated	Paredrine, 20 mg. every half hour from 8:30 a.m. to 6 p.m. Total 400 mg.	Benzedrine, 10 mg. every hour from 8 a.m. to 4 p.m. Total 90 mg.	Benzedrine, 20 mg. at 6 and 7 a.m. Total 40 mg. Paredrine, 40 mg. every 2 hours from 8:30 a.m. to 2:30 p.m. Total 160 mg.		Benzedrine, 20 mg. at 6 and 7 a.m. Total 40 mg.	
	3 p.m.	2:30 p.m.	2:30 p.m.	8:30 a.m.	2:30 p.m.	9 a.m.	3 p.m.
Supine	120/80	125/85	140/95	122/85	150/95	108/76	120/85
Sitting	80/60	115/90	135/90	108/80	138/90	84/55	112/85
Standing	60/?	95/70	98/75	65/50	100/80	50/?	65/55

A comparison of the data tabulated in columns 2 and 3 shows that the pressor effect of paredrine was practically equal to that of benzedrine, but the patient preferred benzedrine because it invigorated and stimulated him, whereas pare-

* Received for publication August 26, 1937.
From the Department of Internal Medicine, State University of Iowa.

drine had no appreciable effect on his lassitude. This suggests that the chronic fatigue which is so characteristic of orthostatic hypotension is not due entirely to the low arterial pressure. No insomnia was produced by paredrine, even with doses as large as 400 mg. a day; contrariwise, it seemed to exert a soporific effect, for the patient not only slept soundly at night, but frequently dozed during the day. The next step was to use benzedrine early in the morning and paredrine throughout the rest of the day, which proved to be the ideal arrangement. After much experimenting with the method of administration, the schedule at the top of column 4 (table 1) was ultimately chosen as the optimum. A comparison of columns 4 and 5 shows the sustaining effect of the paredrine. No unpleasant incidental effects of either drug were noted.

Supplementary Case Report

Throughout the year that had elapsed since our first report,[1] the patient's average daily dose of benzedrine was 80 to 100 mg. Occasionally he increased it to 150 mg. This enabled him to live a quiet life in comfort, but not to do much work. He had been perspiring quite freely, and had noticed that he was no longer entirely impotent or devoid of libido. His basal metabolic rate, originally minus 10 per cent, was now minus 25 per cent. Desiccated thyroid, in doses of 4 grains a day, increased it within 10 days to minus 9 per cent without affecting the blood pressure appreciably.

A previously unrecognized factor in the patient's disability—paroxysmal hypoglycemia—was discovered while he was in the hospital for the paredrine experiment. Our suspicions were aroused when he complained that occasionally he was overtaken rather suddenly by extreme weakness, tremor, nervousness, and hunger which did not seem to him to be due to his orthostatic hypotension because he had noticed that these particular symptoms were unrelated to posture and could always be relieved by the ingestion of food. There was no opportunity to observe the patient during one of these attacks, but 90 minutes after the administration of 50 grams of glucose his blood sugar had fallen to 26 mg. per cent and he was having hypoglycemic symptoms which he recognized at once. Reinvestigation of the history then disclosed the fact that he had had similar seizures many years before. Either they had ceased temporarily or had been overwhelmed by the manifestations of his orthostatic hypotension. That benzedrine might have educed them seemed unlikely. They disappeared entirely when his daily intake of protein was increased from about 75 grams to 120 grams.

We were unable to discover the cause of the patient's increasing anemia. The hemoglobin content of his blood had fallen from 72 to 62 per cent, and the erythrocyte count from 3,790,000 to 2,750,000. There was no history of hemorrhage, the bleeding time and coagulation time were normal, the platelet content of the blood was normal, and the erythrocytes were normally resistant to hemolysis by hypotonic salt solution. The feces were examined for blood many times, but only negligible quantities were found, and roentgenologic examination of the alimentary tract disclosed no evidence of disease. There was no retention of nitrogen in the blood.

Comment

This patient's orthostatic hypotension, paroxysmal hypoglycemia, and low basal metabolic rate suggest the possibility of an endocrine disturbance involving the adrenal, thyroid and pituitary glands and the isles of Langerhans.

Paredrine is a very useful adjuvant to benzedrine in the symptomatic treatment of orthostatic hypotension.

REFERENCES

1. Korns, H. M., and Randall, W. L.: Orthostatic hypotension treated with benzedrine, Am. Heart Jr., 1937, xiii, 114.
2. Alles, G. A.: The comparative physiological actions of the dl-beta-phenylisopropylamines. I. Pressor effect and toxicity, Jr. Pharm. and Exper. Therap., 1933, xlvii, 339.
3. Nathanson, M. H.: Action of parahydroxyphenylisopropylamine on induced cardiac standstill, Proc. Soc. Exper. Biol. and Med., 1937, xxxv, 627.
4. Abbott, W. O., and Henry, C. M.: Paredrine (beta-4-hydroxyphenylisopropylamine). A clinical investigation of a sympathomimetic drug, Am. Jr. Med. Sci., 1937, cxciii, 661.

TOLERANCE TO BENZEDRINE SULFATE*

By Leon J. Robinson, M.D., *Palmer, Massachusetts*

In 1935 Prinzmetal and Bloomberg[1] introduced benzedrine (phenylisopropylamine), a comparatively new sympathomimetic for the treatment of narcolepsy. Its dramatic success in this condition stimulated many investigations of additional therapeutic indications for the use of the systemic effects of benzedrine, as well as verification of its value in narcolepsy.[2] It has been demonstrated that benzedrine relaxes gastrointestinal spasm[3]; ameliorates apathy and depression in normals and in neurotic persons,[4] and in post-encephalitic Parkinsonism[5]; aborts marked drop in blood pressure during spinal anesthesia[6]; and prevents syncope caused by orthostatic hypotension.[7] We have found it efficacious in the prevention of carotid sinus syncope of the vagal and depressor type.[8] No reports of addiction, and only one report of tolerance to benzedrine have been reported to date.[9] In the course of a study on the efficacy of benzedrine sulfate in the control of carotid sinus syncope an appreciable degree of tolerance to benzedrine was elicited. The following case forcibly brought this fact to our attention:

Case Report

A. B., a male patient, 24 years of age, is one of a series of patients with hyperirritable carotid sinus reflex we have been studying. For the past six years this patient has had syncopal attacks occurring about six times monthly. During these attacks there are loss of consciousness and generalized convulsions. The attacks cease within half a minute, and are not followed by confusion. Seizures can be induced by pressure with the fingers over the right carotid sinus. Pressure maintained in this way for 10 seconds causes slowing of the pulse from 70 to 22, decrease in blood pressure from 110 systolic and 70 diastolic to 80 systolic and 60 diastolic and generalized convulsion lasting but six seconds after pressure is released. Atropine gr. 1/60 intravenously was ineffective in preventing induced attacks whereas

* Received for publication September 30, 1937.

epinephrine 0.5 c.c. subcutaneously was efficacious in this regard. This case falls into the type of sinus syncope which Weiss [10] and his colleagues have well classified as embodying both the vagal response (with sino-auricular or auriculo-ventricular block) and the depressor response (with vasodilatation and hypotension). Epinephrine or ephedrine prevents the vagal response by direct ventricular stimulation as a result of which the ventricles assume an independent rhythm sufficiently rapid to prevent the syncope which would otherwise follow vagal heart block. In the depressor type of hyperirritable carotid sinus, these sympathomimetic drugs abort attacks by constricting the small blood vessels, thus abolishing vasodilatation and resulting syncope.[10]

The patient was therefore placed upon ephedrine sulfate therapy which Weiss et al.[10] have demonstrated to be efficacious for the depressor and vagal types of sinus syncope. Although efficacious, the action of ephedrine proved short lived. Generally from ⅜ to ½ grain of ephedrine has been recommended for the depressor type of sinus syncope. But even in one grain doses ephedrine aborted induced attacks for not more than half to one hour in this patient. We therefore resorted to benzedrine, which is a sympathomimetic drug closely related to epinephrine and ephedrine. The patient was given 20 mg. of benzedrine sulfate orally. At intervals attempts were made to induce sinus attacks. It was found that benzedrine prevented cardiac slowing, hypotension and syncope, even when sinus pressure was made, over a period extending from 25 minutes after the oral administration to 4 hours after medication.

Thereafter 20 mg. of benzedrine three times daily prevented induced and spontaneous seizures satisfactorily for 10 days. On the tenth day a spontaneous seizure occurred. We at first were at a loss to account for this as medication had not been interrupted. On attempting pressure over the right carotid sinus, syncope could be induced repeatedly. As a result, 30 mg. of benzedrine sulfate were given thrice daily with again a cessation of spontaneous and induced seizures. This phenomenon recurred several times and the dosage was raised 10 mg. each time. At intervals varying from 7 to 10 days tolerance for the larger doses necessitated repeated increments of benzedrine. At one time the patient was receiving as much as 250 mg. of benzedrine sulfate daily (50 mg. every three hours). Not only was it necessary to increase the individual doses but it became necessary to give the medication at shorter intervals, namely every three hours, as the effects did not persist over the longer period as previously. At this point therapy was withdrawn for several days. Then the initial small doses of benzedrine sulfate which had been effective originally were again administered. Tolerance had disappeared in the interval and the benzedrine was once more as effective as on first administration.

This procedure succeeded in preventing spontaneous and induced seizures for another week to ten day interval. After this time tolerance reappeared, and it was necessary either to raise the dosage or omit the benzedrine for two to three days, and then renew the small doses.

Although insomnia was present for the first night, benzedrine thereafter did not interfere with sleep even when given in large doses.

Comment

The greater number of observers who have reported on the systemic use of benzedrine have failed to note the development of tolerance. Solomon, Mitchell and Prinzmetal [5] "have seen no evidence to indicate either an increasing tolerance to the drug or habit formation." As much as 160 mg. a day for three weeks was taken by one of their patients without apparent harmful effect. They make the interesting statement that the first patient with narcolepsy reported by Prinzmetal and Bloomberg [1] is still taking the same dose after three years.

Nevertheless, as in this case, those who have given benzedrine invariably comment on the fact that it often causes insomnia at the outset.[1, 4, 5] This disappears in a few days (generally one to three days) despite continuance of the initial dosage. Solomon and his colleagues[5] stated that 11 of their postencephalitic patients did not sleep well the first few nights following the beginning of benzedrine treatment but that the relative insomnia usually lasted no more than three days and usually wore off without the necessity of reducing the dosage.

Furthermore they noted that dizziness or undue nervous tension which appeared for a day or two at the beginning of treatment in six cases, recurred in three cases when the dosage was increased later, but was only temporary. Excessive restlessness and excitement occurring temporarily in two cases were eliminated by halving the dose, and even when the dosage was raised later these symptoms did not reappear. We interpret these facts as evidence of tolerance to benzedrine's undesirable effects, although we are fully cognizant that these observers noted no tolerance to the desired therapeutic effect of benzedrine such as is reported here.

Davis and Shumway-Davis treating a case of orthostatic hypotension with benzedrine found it necessary, after a time, to increase the previously effective benzedrine doses, and their other case so treated in whom "all symptoms had disappeared," later increased his benzedrine dosage himself because the additional doses made him feel "more comfortable."[7]

Wilbur et al.[9] reported that, while benzedrine abolished the apathy in many patients suffering from a state of chronic exhaustion, in an appreciable number of these patients the beneficial effects of the benzedrine wore off at the end of 3 to 16 weeks of continued administration of the drug. In their group of 21 psychoneurotic depressed patients benefited by benzedrine, "six reported that in spite of continued medication the initial favorable results were not repeated after the first week. Because benzedrine failed to relieve their condition, an additional six patients discontinued its use in one month and three more patients discontinued its use at the end of three months."

Much like our experience with the reported case, Wilbur et al.[9] also found that occasionally, intermittent use of benzedrine proved more satisfactory than continuous administration.

SUMMARY

An instance of tolerance to benzedrine sulfate is reported. Benzedrine sulfate was initially effective in preventing the depressor type of response and syncope due to a hyperirritable carotid sinus in a male of 24.

Tolerance to benzedrine, exemplified by recurrence of sinus hyperirritability, developed on the tenth day.

Thereafter at 7 to 10 day intervals it was necessary either to increase the dosage or omit the drug for several days in order to maintain the therapeutic efficacy of benzedrine.

REFERENCES

1. PRINZMETAL, M., and BLOOMBERG, W.: The use of benzedrine for the treatment of narcolepsy, Jr. Am. Med. Assoc., 1935, cv, 2051–2054.
2. ULRICH, H., TRAPP, C. E., and VIDGOFF, B.: The treatment of narcolepsy with benzedrine sulfate, ANN. INT. MED., 1936, ix, 1213–1221.

3. Myerson, A., and Ritvo, M.: Benzedrine sulfate and its value in spasm of the gastrointestinal tract, Jr. Am. Med. Assoc., 1936, cvii, 24–26.
4. Myerson, A.: Effect of benzedrine sulfate on mood and fatigue in normal and in neurotic persons, Arch. Neurol. and Psychiat., 1936, xxxvi, 816–822.
5. Solomon, P., Mitchell, R. S., and Prinzmetal, M.: The use of benzedrine sulfate in postencephalitic Parkinson's disease, Jr. Am. Med. Assoc., 1937, cviii, 1765–1770.
6. Tovell, R. M.: Control of blood pressure during spinal anesthesia: preliminary report, Proc. Staff Meet. Mayo Clinic, 1936, ii, 585–588.
7. Davis, P. L., and Shumway-Davis, M.: Orthostatic hypotension: the treatment of two cases with benzedrine sulfate, Jr. Am. Med. Assoc., 1937, cviii, 1247–1249.
8. Robinson, L. J.: Benzedrine sulfate in the treatment of syncope due to a hyperactive carotid sinus reflex, New Eng. Jr. Med., 217 (to be published).
9. Wilbur, D. L., MacLean, A. R., and Allen, E. V.: Clinical observations on the effect of benzedrine sulfate, Jr. Am. Med. Assoc., 1937, cix, 549–554.
10. Weiss, S., Capps, R. B., Ferris, E. B., Jr., and Munro, D.: Syncope and convulsions due to a hyperactive carotid sinus reflex, Arch. Int. Med., 1936, lviii, 407–417.

PRIMARY SARCOMA OF THE PERICARDIUM; REPORT OF A CASE *

By P. G. Boman, M.D., F.A.C.P., *Duluth, Minnesota*

Primary tumors of the heart and pericardium are rare, and a definite diagnosis of such a condition is seldom made except at autopsy. In reviewing this subject, Yater [1] states that more than 150 cases of primary tumor of the heart have been reported in the literature, and Lymburner [2] in 1934 found 256 such cases recorded. While there is some difference of opinion as to the number of authenticated cases reported, it is evident that these cases are not common and that they are of considerable medical interest.

The great majority of the reported primary tumors are benign. Less than 20 per cent are malignant. Of the malignant group almost all the cases reported are of primary sarcoma of the heart and pericardium. In view of this it is interesting to note that Perlstein [3] in 1918 found only 30 cases of primary sarcoma recorded, and added 1 additional case of his own. Yater [1] in 1931 stated that 15 additional cases had been reported in the interim. Since that time, in this country, Morris [4] in 1933, and Barnes, Beaver and Snell [5] in 1934, reported two additional cases. Of these reported cases, 15 were spindle cell sarcomata, 14 round cell sarcomata, 4 giant cell sarcomata, 3 myxosarcomata, 3 fibrosarcomata, 4 mixed cell sarcomata, 1 angiosarcoma, 1 lymphosarcoma, 1 liposarcoma and 1 rhabdomyosarcoma.

From the reports in the literature it is apparent that the majority of sarcomata of the heart arise from the auricles and that relatively few originate in the pericardium, only 10 having been reported as primary in the pericardium according to Yater's [1] review.

The symptomatology of tumors of the heart varies greatly. In some instances symptoms of cardiac origin are not present up to the time of death, while in others symptoms of cardiac involvement and cardiac failure appear at varying times before death. Sudden deaths, both with and without previous

* Presented at the meeting of the Minnesota Heart Society, December 7, 1935.
From the Department of Medicine, The Duluth Clinic.

cardiac symptoms, are reported, and symptoms suggestive of subacute bacterial endocarditis have been recorded. Arrhythmias and conduction disturbances likewise may be present. Naturally, the symptoms will vary according to the location of the tumor and the portion of the heart which is primarily involved. In order to classify the symptomatology, Yater [1] has used the following division of symptoms:

(*A*) Clinical types not suggestive of tumor of the heart:

1. Absence of symptoms referable to the heart.
2. Symptoms of cardiac embarrassment terminally.
3. Symptoms of congestive heart failure.
4. Sudden death.
5. Symptoms suggestive of subacute bacterial endocarditis.

(*B*) Clinical types suggestive of tumor of the heart:

1. Heart block.
2. Symptoms referable to location of tumor other than heart block.
3. Symptoms of cardiac dysfunction developing without apparent cause in a patient with a known malignant process.
4. Accumulation of hemorrhagic fluid, pericardial and pleural.
5. Suggestive roentgen observations.

This division is of particular value in the study of the reported cases. Actually few symptoms are found which are constant and of diagnostic help.

In primary malignant growth of the pericardium one may find many of the symptoms usually associated with pericarditis, and the course of the former may so closely simulate that of the latter as to lead to a diagnosis of pericarditis, as occurred in the case herewith reported. There does not appear in the literature any case of primary malignant neoplasm of the pericardium which has been diagnosed ante mortem.

Case Report

History: A white male, aged 27, was first seen on April 1, 1931, at which time he complained of precordial pain and palpitation of the heart of one month's duration. Immediately preceding the onset of these symptoms he had an attack of "influenza" lasting one week. During convalescence he cranked a car, after which he felt very weak and short of breath, his heart beat rapidly and he noticed a generalized soreness and stiffness of the chest and of the right shoulder. After one week the soreness and stiffness disappeared, but attacks of pain in the precordium, with radiation to the right shoulder, continued and increased in frequency and severity. The pain was of a pressure type, and the patient stated that it felt like "a ton of bricks was laid on my chest." He noted that the pain was increased on swallowing and after exercise. Night sweats were present, his appetite became poor, and there were indications of weight loss.

Past History: Except for measles in childhood and tonsillectomy there was no history of any previous illnesses.

Family History: Father living and well. Mother living but has diabetes mellitus. One brother living and well. One aunt has pulmonary tuberculosis; one cousin died of pulmonary tuberculosis.

Marital History: Married; wife and two children living and well.

Physical Examination: General development was good. There was no evidence of recent weight loss.

Head and Neck: No abnormalities noted.

Chest: No abnormal impulses were seen and the percussion note over the lung areas was normal. The apex beat of the heart was just outside of the nipple line, and the percussion outline indicated enlargement of the heart, both to the left and to the right. The heart tones were regular and strong. A pericardial rub was heard in the third and fourth interspaces to the left of the sternum during systole and diastole. The breath sounds were normal and no râles were heard. The blood pressure was 130 systolic and 80 diastolic.

Abdomen: Negative on palpation and percussion.

Extremities: Negative.

Laboratory Data: The hemoglobin was 92 per cent, leukocytes 9,500. The urinalysis was negative chemically and microscopically. The Wassermann reaction was negative. An electrocardiogram showed an auricular and ventricular rate of 80, with a PR interval of 0.14 second; there was a slight elevation of the ST interval, with a beginning downward deflection of the T-wave in the first lead.

A tentative diagnosis of pericarditis was made and hospitalization advised.

The patient, however, remained at home and symptoms continued to increase until the evening of April 23, when he noted a sudden aggravation of his precordial pain. This was followed by marked pallor, weakness and unconsciousness. When seen shortly afterwards the heart action was very feeble. He had alternating extrasystoles, coming very close to the preceding beat, and insufficiently strong to be recorded in the radial pulse, giving the impression of a marked bradycardia. His blood pressure was 80 systolic and 60 diastolic. No congestive râles were noted in the lungs, but the liver was slightly enlarged and tender. He was brought to St. Mary's Hospital, where he remained during the subsequent course of his illness.

Shortly after admission to the hospital his temperature was 99°, and varied between this point and 101.8° during the next three weeks, after which the temperature was normal or subnormal up to the time of his death, which occurred on June 16. The heart rate was seldom over 80 beats per minute until the last two weeks, when definite cardiac failure developed. The pain continued and the pericardial rub was present, until about two weeks ante mortem.

Urinalysis was consistently negative. The leukocyte count ranged from 11,800 to 16,000. The differential white count showed a variation from 61 to 81 per cent polymorphonuclears, 14 to 35 per cent lymphocytes, 2 to 4 per cent transitionals, and an average of 1 per cent eosinophiles. The hemoglobin ranged between 85 and 93 per cent, and the red blood count from 4,200,000 to 4,670,000.

A stereo roentgenogram (figure 1 a) of the chest made on May 11, 1931 indicated a generalized cardiac enlargement, but no evidence of pulmonary or pleural involvement. A single roentgenogram (figure 1 b) of the chest made on May 25, 1931 showed that the cardiac outline was slightly larger than that previously noted, and was suggestive of a moderate pericardial effusion. The left costophrenic angle was obliterated and there was indication of a thickening of the pleura of the entire left lung.

An electrocardiogram (figure 2 a) on May 12, 1931 showed an auricular and ventricular rate of 90, with a PR interval of 0.14 second. There was a deep inversion of the T-wave in Leads I and II, with a decreased amplitude of the T-wave in Lead III. An electrocardiogram (figure 2 b) on May 23, 1931 revealed an auricular and ventricular rate of 100, with a PR interval of 0.16 second, an elevation of the ST interval in Leads I and II, with a downward deflection of the T-wave in these same leads, and a definite right axis deviation.

One consultant suggested a subacute bacterial endocarditis or a tuberculous mediastinitis as the basis for the symptoms presented. (A blood culture failed to show any growth and a Mantoux reaction was absent.)

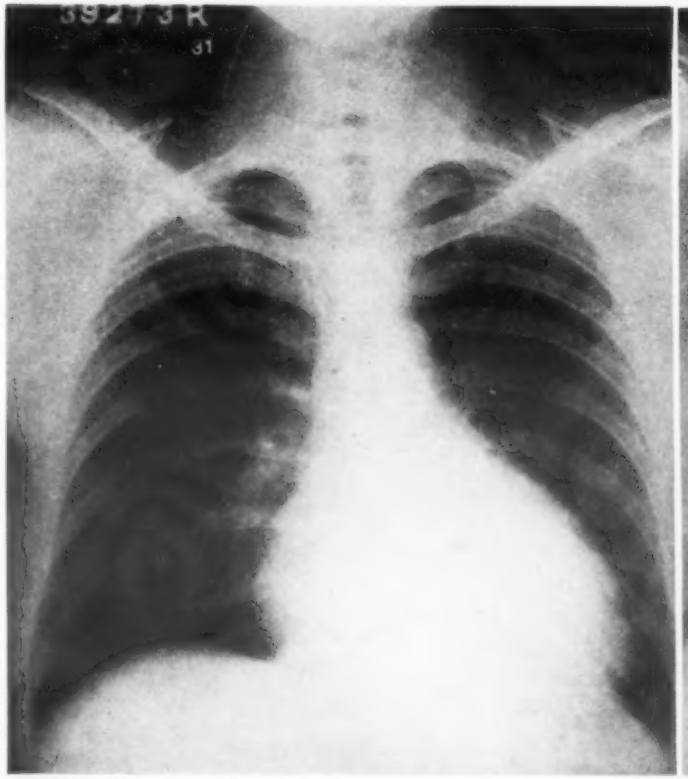


FIG. 1 a. Roentgenogram of chest, taken two months after the onset of symptoms, indicates a generalized cardiac enlargement.

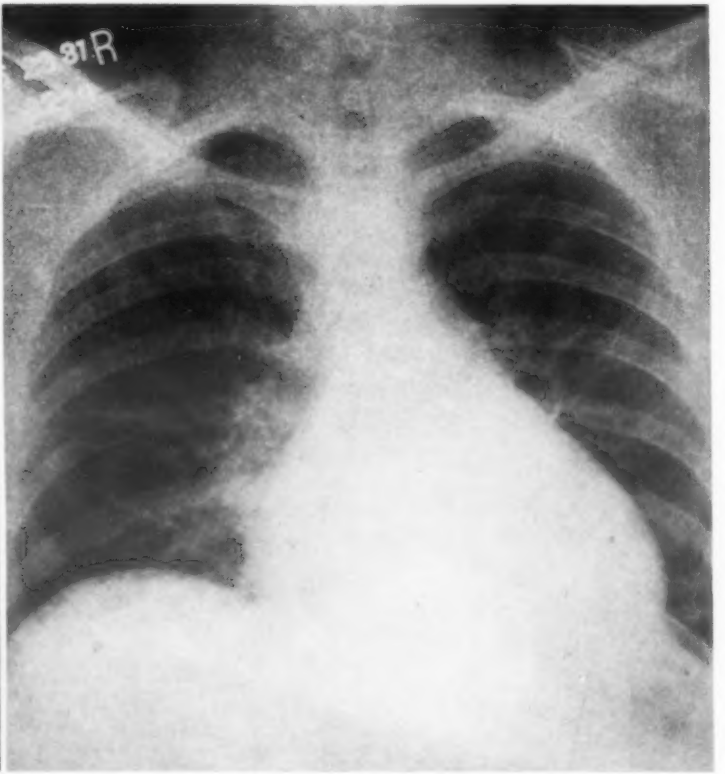


FIG. 1 b. A progressive enlargement of the heart is noted in this roentgenogram, taken one month later.

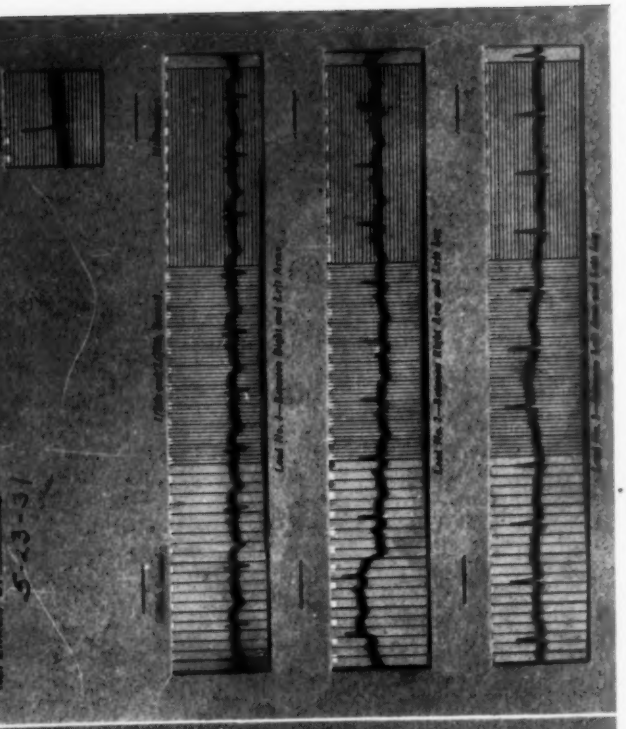


FIG. 2b. Electrocardiogram taken one month later shows elevation of the ST intervals in Lead I, with inverted T-waves in Leads I and II, closely simulating the electrocardiograms obtained in cases of recent coronary thrombosis.

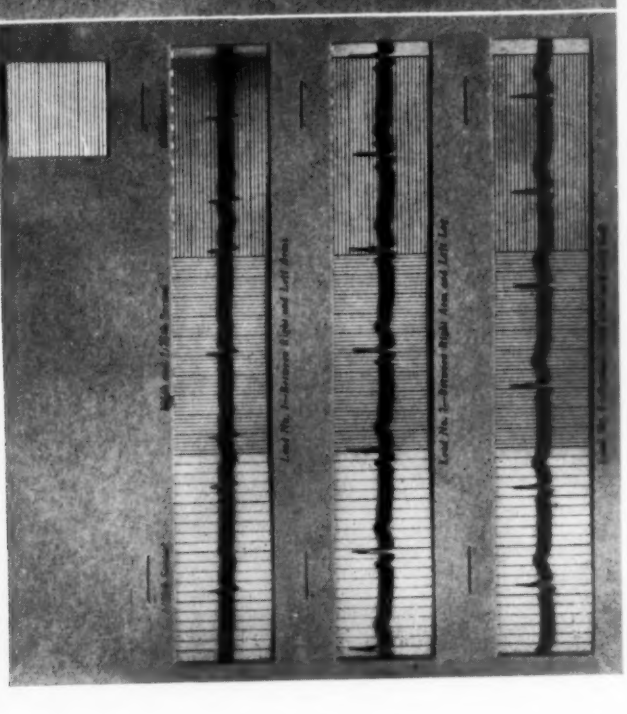


FIG. 2a. Electrocardiogram on April 24 shows beginning inversion of the T-waves, with moderate upward convexity of ST intervals in Lead I. Auricular extrasystoles are present.

The patient died on June 16, 1931.

Necropsy Findings: The necropsy was performed by Dr. G. L. Berdez, pathologist at St. Mary's Hospital, and the following is based on his report:

The body measured 172 cm. in length and was in a moderately good state of nutrition. There was a marked edema of the legs, thighs and of the external genitalia, as well as a moderate distention of the abdomen.

On opening the thorax it was noted that the cavity of the pericardium was completely obliterated by grayish-white tumor masses, which glued together the visceral

FIG. 3. Photograph of gross specimen shows the extensive involvement of the visceral and parietal pericardium.

and parietal layers of the pericardium. It was with difficulty that the pericardial adhesions could be separated, and most of the tumor masses remained attached to the epicardium (figure 3). These tumor masses were very hard and measured up to 1 cm. in thickness, and in places infiltrated the more superficial layers of the myocardium. They were grayish-white, friable, and showed areas of necrosis. Almost the entire surface of the visceral and parietal layers of the pericardium was covered with the tumor tissue, which also completely surrounded the base of the aorta and the first part of the pulmonary artery, rendering them quite rigid. The mitral and tricuspid valves were patent for two fingers; the aortic and pulmonary valves were com-

petent. There were a few yellowish spots on the mitral valves, but no further deposits were noted on the valves or on the endocardium. The myocardium was brownish red and somewhat edematous. The heart weighed 800 gm. Several small lymph glands around the arch of the aorta were found to be extensively invaded by the tumor tissue.

The right pleural cavity contained 2,000 c.c. of clear serous fluid, and no adhesions were noted, while the left pleural cavity contained 1,000 c.c. of clear serous

FIG. 4. Photomicrograph of the pericardium—low power magnification.

fluid, and several fibrous adhesions were noted over the upper left lobe. The right and left lungs weighed respectively 325 and 430 gm. A large hemorrhagic infarct was noted in the lower left lobe, and in the corresponding branch of the pulmonary artery was a moderately large embolus.

The lung tissue as a whole was congested and edematous. No evidence of metastatic invasion was noted in the lungs, in the peribronchial or tracheal lymph glands.

The abdominal viscera were essentially negative except for evidence of chronic congestion. (No evidence of metastatic malignancy was found.)

Microscopic examination of the tumor masses (figures 4 and 5) of the pericardium showed that the tumor tissue was formed by spindle cells which infiltrated diffusely the tissue of the pericardium, including the subserous layers. In certain areas the tumor tissue extended to the superficial layers of the myocardium. Small round spaces could be recognized here and there in the tumor tissue, representing

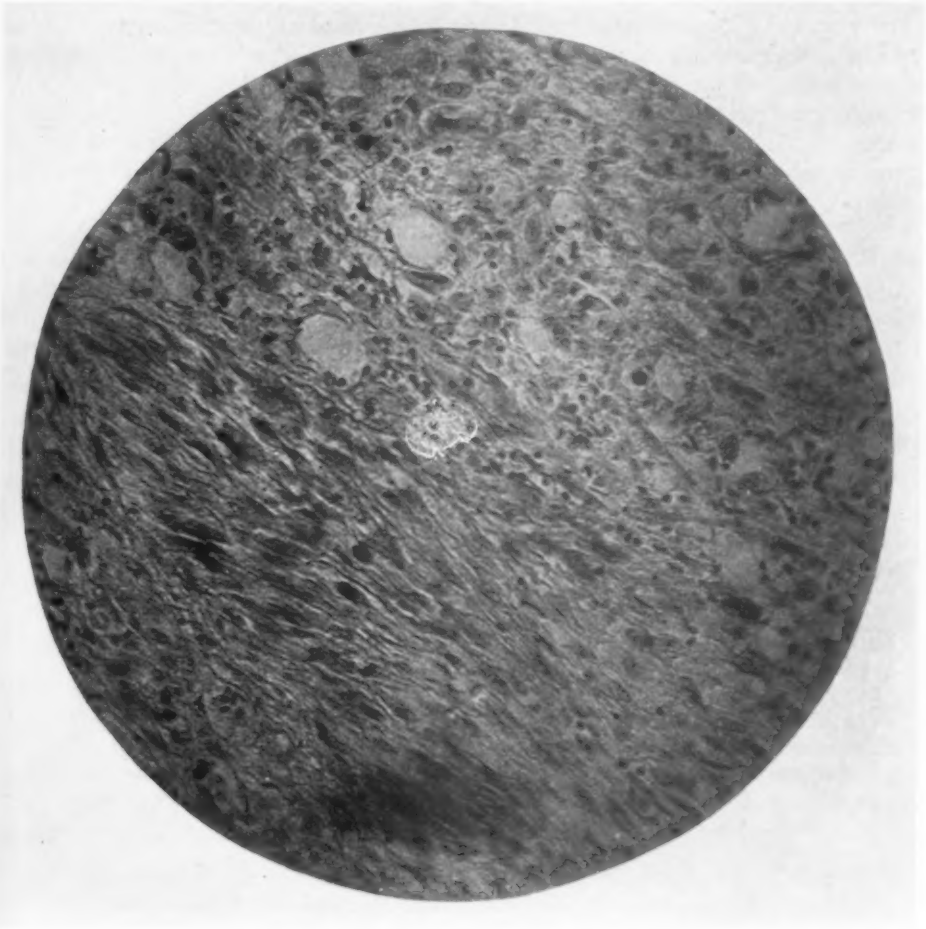


FIG. 5. Photomicrograph of pericardium.

what was left of the adipose tissue of the subepicardial layers. The tumor cells were arranged in bundles, pointing in various directions, and large areas of tumor tissue were completely necrotic. The tumor cells showed a marked irregularity in shape and size, and contained nuclei which were generally elongated, moderately rich in chromatin, occasionally multiple, and at times showing mitotic figures. In certain sections groups of tumor cells filled the smaller veins and lymphatics, and in the myocardium adjacent to the tumor tissue areas of lymphocytic infiltration were noted.

The lymph glands located at the arch of the aorta showed extensive replacement by tumor tissue having a structure similar to that noted in the pericardium.

A diagnosis of spindle cell sarcoma of the pericardium was made by Dr. Berdez.

Comment

The necropsy findings indicate a case of primary sarcoma of the pericardium, involving extensively the visceral and parietal pericardium to the extent that the pericardial cavity was entirely obliterated by a fusion of the tumor masses. There was only a moderate invasion of the myocardium, and the only evidence of metastatic invasion was found in the small lymph glands around the arch of the aorta. The physical and roentgen findings supported a diagnosis of pericarditis, and gave no clue as to the true etiological factor underlying the disease process. The electrocardiographic records are of considerable interest in that they closely resembled the electrocardiographic records obtained in cases of recent coronary thrombosis. They showed the presence of progressing myocardial disease, but nothing which could be considered characteristic or diagnostic of a malignant condition. It is the opinion of several authors (Willius and Amberg,[6] Siegel and Young,[7] Houck and Bennett [8]), that electrocardiograms in primary or secondary tumors of the heart do not show any findings which are characteristic of the malignant conditions but rather simulate the electrocardiographic findings associated with myocardial changes from other causes.

Conclusions

A case of primary sarcoma of the pericardium with physical, roentgenographic, electrocardiographic and necropsy findings has been presented, to be added to the relatively small number of cases previously reported.

BIBLIOGRAPHY

1. Yater, W. M.: Tumors of the heart and pericardium; pathology, symptomatology and report of nine cases, Arch. Int. Med., xlviii, 627–666.
2. Lymburner, R. M.: Tumours of heart: histopathological and clinical study, Canadian Med. Assoc. Jr., 1934, xxx, 368–373.
3. Perlstein, I.: Sarcoma of the heart, Am. Jr. Med. Sci., 1918, clvi, 214.
4. Morris, J. J.: Primary sarcoma of heart, Jr. Lab. and Clin. Med., 1933, xviii, 935–940.
5. Barnes, A. R., Beaver, D. C., Snell, A. M.: Primary sarcoma of the heart; report of case, with electrocardiographic and pathologic studies, Am. Heart Jr., 1931, ix, 480–491.
6. Willius, F. A., and Amberg, S.: Two cases of secondary tumor of heart in children, in one of which diagnosis was made during life, Med. Clin. N. Am., 1930, xiii, 1307–1316.
7. Siegel, M. L., and Young, A. M.: Electrocardiographic findings in tumors of the heart, Am. Heart Jr., 1933, viii, 682.
8. Houck, G. H., and Bennett, G. A.: Polypoid fibroma of left auricle (so-called cardiac myxoma) causing ball valve action, with report of case, Am. Heart Jr., 1930, v, 787–794.

EDITORIALS

THE EXPERIMENTAL PRODUCTION OF HYPERTENSION

THE question of the etiology of chronic renal disease and of the cardiovascular lesions commonly associated with it has long interested investigators, and many attempts have been made to reproduce these conditions in animals. Although some of these efforts have met with a measure of success, hitherto the experimental disease has never closely duplicated that seen in man. An important advance toward a solution of some phases of this problem has recently been accomplished through the work of Goldblatt and his associates.[1]

These investigators were the first to reproduce in animals a condition closely resembling essential hypertension in man. This they accomplished in dogs, and later in monkeys, by producing renal ischemia by partially clamping off one or both main renal arteries. They were able to control the severity of the disease produced by varying the degree to which the arteries were constricted. By causing moderate obstruction of one or both arteries, a sustained benign type of hypertension was produced. In animals in which only one artery was partly obstructed, the hypertension tended to subside after varying intervals, whereas in others in which both renal arteries were so treated, it persisted indefinitely, in some animals for more than five years. These animals usually showed no evidence of impairment of renal function by the ordinary clinical tests and seemed normal in other respects. No detailed description of the lesions found in these animals has yet been published, but thickening of the media and thickening and hyalinization of the intima of the retinal and other systemic arterioles are mentioned.

If the ischemia was relieved by releasing the clamp, the hypertension promptly subsided. The hypertension could not be prevented or relieved by such procedures as bilateral sympathectomy, or section of the anterior spinal nerve roots. If the ischemic kidney was removed, however, the blood pressure fell promptly to normal provided that the other kidney had not been injured. Removal of both kidneys or complete occlusion of all the renal vessels does not cause hypertension. Such facts led Goldblatt [2] to the conclusion that the hypertension must be due to the action of some humoral substance which is produced in the kidney tissue when damaged by ischemia. Nothing definite is yet known as to the nature of this "hypothetical effect substance," or as to the mechanism by which it produces the hypertension except that some adrenal cortex must be present.

[1] GOLDBLATT, H., LYNCH, J., HANZAL, R. F., and SUMMERVILLE, W. W.: Studies on experimental hypertension. (I) The production of persistent elevation of systolic blood pressure by means of renal ischemia, Jr. Exper. Med., 1934, lix, 347.

[2] GOLDBLATT, H.: Studies on experimental hypertension. (V) The pathogenesis of experimental hypertension due to renal ischemia, ANN. INT. MED., 1937, xi, 69.

More recently Goldblatt [3] has reported the production of a malignant type of hypertension by more markedly constricting both renal arteries. These animals showed a very high blood pressure and quickly developed evidences of grave renal insufficiency with elevation of the non-protein nitrogen and creatinine in the blood. After varying intervals they became anuric, developed convulsions and coma and died in uremia. At necropsy the most striking findings consisted of numerous petechial hemorrhages caused by focal lesions in the capillaries and arterioles. The arterioles showed a deposition of hyalin beneath the intima and areas of necrosis. These lesions were regarded as identical, except for their greater severity, with those found in human cases of malignant hypertension. They were found in the systemic vessels in many areas, but not, however, in the kidneys. Their production apparently depends upon both the presence of a humoral toxic substance and a high tension within the vessels.

In some animals intermediate types of disease were produced: sustained hypertension with at first slight impairment of renal function, and later, perhaps after a long interval, grave renal insufficiency and death in uremia.

Much of Goldblatt's work has already been confirmed by other investigators.[4]

This work has an evident application only to certain phases of renal disease in man. It offers no obvious help in explaining the production of diffuse glomerular nephritis of infectious origin. If hypertension in man is also a result of renal ischemia, the site of the obstruction to the circulation must be in the small vessels, particularly the preglomerular arterioles. The fundamental cause of these arteriolar changes remains obscure. In spite of these limitations, however, such experiments provide new and promising methods of approach to many problems concerning hypertension, and they should help to rationalize the treatment of this serious condition.

P. C.

POSTMORTEM EXAMINATIONS

In this issue Dr. Alan Gregg has drawn attention to the value to the patient of demanding of his physician that a post mortem be performed in the event of his death. This highly original and valuable contribution to our thinking on this subject deserves wider circulation among the laity than it will receive through the pages of the Annals. The most effective method of spreading this doctrine would be for individual physicians to give to their patients a reprint of Dr. Gregg's address to the College. With Dr. Gregg's permission arrangements have been made therefore whereby any

[3] Goldblatt, H.: Studies on experimental hypertension. (VII) The production of the malignant phase of hypertension, Jr. Exper. Med., 1938, lxii, 809.

[4] Child, C. G.: Observations on the pathological changes following experimental hypertension produced by constriction of the renal artery, Jr. Exper. Med., 1938, lxii, 521.

practicing physician can order such reprints direct from the Lancaster Press, Lancaster, Pennsylvania.*

In the discussion of the pros and cons of State Medicine the present system of medical care is frequently attacked on the ground that it includes no method of supervision of the competency of the practitioner. Our position in this respect would be a stronger one if we could say that the quality of the medical care we offer cannot urgently need revision in the cases which have recovered, and that we advocate and work towards the goal of 100 per cent of autopies of fatal cases as the best corrective of defects in our knowledge, skill or judgment.

* The cost may be computed by reference to the paragraph on Reprints on the back cover of this journal.

REVIEWS

The Therapeutic Problem in Bowel Obstruction. By OWEN H. WANGENSTEEN, M.D., Ph.D. 360 pages; 17 × 25.5 cm. Charles C. Thomas, Springfield, Ill. Price, $6.00.

This summary of the author's many investigations and experiences on the subject of intestinal obstruction is a small book of definite value. The practical utility of the book will be appreciated by the physician, the surgeon and the researcher. The bibliography contains generous quotations of more than one thousand authors.

Dr. Wangensteen points out the "slender support by recent researches of the toxic theory" and demonstrates with persuasive eloquence the increasing evidence that mechanical factors are essential elements determining the mortality rate.

Therapeusis guided along these lines has reduced the mortality rate and "supports the denial of the fatality resulting from toxic absorption." At the same time, the suction method is not construed to be the choice of procedure in all cases of obstruction. "Operation still is and possibly will continue to be the chief mainstay of therapy in most forms of bowel obstruction. It is, however, apparent that some cases need not be operated upon, particularly patients with partial obstruction of the small intestine." Early operation is the choice in strangulation obstructions.

C. F. H.

Pocket Atlas of Anatomy. By VICTOR PAUCHET and S. DUPRET. 3rd edition. 368 pages; 12 × 18.5 cm. Oxford University Press, New York. 1937. Price, $4.00.

Containing 345 plates and condensed to very convenient proportions this "Pocket Atlas of Anatomy" covers almost as much ground as its fellows of larger size. Although the plates are relatively small they are clear, detailed, well-labelled and not over-crowded. Each region is adequately dealt with and cross sections are included where important relations are to be demonstrated. There is no abbreviated text such as often detracts from the merits of other atlases. The terminology is that "adopted by the Anatomical Society at Birmingham in 1933; but where the names differ markedly from the Basle Nomina Anatomica, the B.N.A. are retained in square brackets," which makes the book reasonably adaptable to all schools. The hope expressed on the fly-leaf that "this Pocket Atlas of Anatomy will be of service not only to students but to general practitioners and surgeons on account of its handiness and simplicity" has a fair chance of fulfillment if it is realized that books of its calibre are to be used in conjunction with textbooks and dissecting room study and not as a substitute for either.

M. E.

Clinical Roentgen Therapy. Edited by ERNEST A. POHLE, M.D., Ph.D., F.A.C.R., Professor of Radiology; Chairman, Department of Radiology and Physical Therapy, University of Wisconsin, Madison, Wisconsin. 819 pages; 15 × 24 cm. Lea & Febiger, Philadelphia. 1938. Price, $10.00.

This work constitutes an edition of chapters contributed by seventeen specialists of the United States, Canada, and Europe and represents the first real attempt to assemble the vast store of knowledge of roentgen therapy into a volume for the English speaking radiologists. Attempts to produce such a volume previous to this time have been fraught with discouragement due to the rapid changes that have been

taking place in this branch of medicine. With the standardization of the international "r" unit, the improvement of apparatus, the standardization of technics, and the ability to duplicate and check the results of investigators, the specialty of radiology has become more stabilized. A tremendous amount of material has been condensed by the authors who have maintained a keen sense of discrimination between that which is worthy and that which will not withstand the scrutiny of medical science. A multitude of conditions have been treated by the roentgen-rays and an honest effort has been made to evaluate the claims of over-enthusiastic workers.

The clinical aspect of many conditions considered has been included, a feature which makes for interest, completeness, and logic in comprehending the problems involved in the treatment of malignancy and infections. Controversies have not been included since details would defeat the purpose of the book. The extensive bibliography furnishes the reader with a supply of material for reference if he desires further information.

The editor uses occasional helpful foot-notes to explain, clarify, and correlate the writings of the foreign specialists with those of the American.

Because of the combined use of radium and roentgen-rays in certain conditions an adequate discussion of the use of the former is included in spite of the limitation suggested in the title. This volume can be recommended as an invaluable guide for every roentgenologist.

H. J. W.

Clinical Urinalysis. By ROBERT A. KILDUFFE, A.M., M.D., F.A.S.C.P. 428 pages; 23 × 14.5 cm. F. A. Davis, Philadelphia, Pa. 1937. Price, $4.00.

This is a concise and comprehensive treatment of the subject of urinalysis intended for the use of the practicing physician. The text is well planned. There is a short history of the subject and a brief discussion of the anatomy and physiology of the kidneys. The major portion of the book is devoted to the composition of urine and the better methods of analysis available with interpretations of results. The author has also included an outline of equipment and reagents necessary for setting up an office laboratory. The book is not only of value to the physician who makes his own analyses but also to those who must interpret the reports from clinical laboratories.

E. M. R.

Die physiologische und klinische Bedeutung des Blutammoniaks (Physiological and Clinical Significance of Blood Ammonia). By LAZAR STANOJEVIĆ, M.D. 64 pages; 16 × 23.5 cm. Theodor Steinkopff, Dresden and Leipzig. 1938. Price, RM 6.

This small monograph is essentially a critical survey of the literature (213 references) on the determination of the ammonia content of the blood and its significance in physiology, pathology and medicine. The author himself is an active investigator in this field. Workers engaged in research on this subject or individuals desiring detailed information on blood ammonia should find this book invaluable.

E. G. S.

Practical Methods in Biochemistry. By FREDERICK C. KOCH. Second edition. 302 pages; 16.5 × 23.5 cm. William Wood and Co., Baltimore. 1937. Price, $2.25.

This laboratory manual is divided into three parts. Part I (74 pages) deals with experiments on carbohydrates, lipins, proteins and hydrogen-ion concentration; Part II (26 pages) describes experiments on salivary, gastric and intestinal digestion, and Part III (124 pages) deals with qualitative and quantitative

experiments on blood and urine. Concise but adequate directions are given for 232 experiments.

"Although this manual is intended primarily as the practical companion to Professor Matthew's textbook, nevertheless it contains considerable explanatory matter," a feature which appeals particularly to the reviewer, "in order to help correlate the theoretical and laboratory aspects of the subject matter." Since over half of the experiments are devoted to blood and urine chemistry, the book should prove valuable not only to medical students but to hospital laboratory workers and clinical chemists as well. "However no attempt has been made to interpret the significance of the results in blood and urine analysis." Although the experiments and methods are well selected and clearly described, the reviewer feels that a few typical experiments on bio-colloid chemistry would be helpful additions to an otherwise valuable book. It is well printed and well bound and the subject matter is attractively presented to the eye by means of the variation in the size of the print. An index and adequate references to the original literature are included. A large and informative appendix (63 pages) containing an extensive list of reagents and solutions and detailed directions for their preparation, frequently including an exposition of the chemical principles involved, adds materially to the value of this laboratory manual.

E. G. S.

COLLEGE NEWS NOTES

Gifts to the College Library

Acknowledgment is made of the receipt of the following gifts to the College Library of publications by members:

Reprints

Dr. Guy W. Carlson, F.A.C.P., Appleton, Wis.—one reprint, "An Outbreak of Trichiniasis in East Central Wisconsin";

Dr. Norbert Enzer, F.A.C.P., Milwaukee, Wis.—one reprint, "Chronic Lung Changes in Electric Arc Welders";

Dr. A. Allen Goldbloom, F.A.C.P., New York, N.Y.—two reprints, "Schmincke's Tumor (Lympho-Epithelioma) with Metastases Complicated by Tracheo-Esophageal Fistula" and "Clinical Studies in Circulatory Adjustments. IV. Obliterating Pulmonary Arteritis with Secondary Pulmonary Changes and Right Ventricular Hypertrophy; Report of a Case with Autopsy";

Dr. Ernest E. Hadley (Associate), Washington, D. C.—two reprints, "The Psychoanalytic Clarification of Personality Types" and "Unrecognized Antagonisms Complicating Business Enterprise";

Dr. Florimond J. LeBlanc (Associate), Elgin, Ill.—one reprint, "Oxidation Reduction in Colloidal Chemistry";

Dr. Lowell S. Selling, F.A.C.P., Detroit, Mich.—two reprints, "The Endocrine Glands and the Sex Offender" and "Un Tipo Especial De Homosexualidad Encontrado En Las Escuelas Correccionales De Niñas."

Sectional Meeting of Florida Members

Fellows and Associates of the American College of Physicians residing in Florida have organized an informal group for the purpose of closer acquaintanceship and a better opportunity to share each other's progress. They meet once each year on the day previous to the Florida State Medical Society meeting and in the same city. Fellows and Associates residing in or near the city in which the meeting is to be held have charge of the program, which consists of short clinical discourses in the forenoon, round table luncheon and a general visit and get-together in the afternoon. The organization is entirely informal, there being no by-laws and the expense is prorated by the members who attend each year.

The first meeting was held at Miami, May 9, 1938. Dr. P. B. Welch, F.A.C.P., Miami, was the first chairman and Dr. Kenneth Phillips, F.A.C.P., Miami, was the first secretary. Program was as follows:

"Contagious Diseases of Childhood: Immunization and Modification," Dr. Warren Quillian, F.A.C.P., Coral Gables;

"Differential Diagnosis of Chest Pain," Clinic, Dr. E. Sterling Nichol, F.A.C.P., Miami;

"Modern Treatment in Diabetes Mellitus," Dr. Arthur Walters (Associate), Miami Beach;

"Advances in Fever Therapy by Physical Means," Motion Picture Demonstration, Dr. Kenneth Phillips, F.A.C.P., Miami.

This was followed by a round table luncheon; there were fifty-five members in attendance.

Meeting of Puerto Rico Members

On June 12, 1938, Dr. and Mrs. R. Rodriguez-Molina tendered a dinner party to the members of the American College of Physicians resident in Puerto Rico at their country home in Hato Tejas, Bayamón. The dinner was given in honor of Dr. Ramón M. Suárez, F.A.C.P., Governor of the College for Puerto Rico. Dr. Suárez gave a report to the members on the annual meeting of the College held in New York during April. The following were present:

Dr. and Mrs. R. Rodriguez-Molina
Dr. and Mrs. Ramón M. Suárez
Dr. and Mrs. César Domínguez
Dr. and Mrs. Guillermo Marquez
Dr. and Mrs. Juan Sabater
Dr. and Mrs. Luis Morales
Dr. and Mrs. Enrique Koppisch
Dr. and Mrs. Arturo Carrión
Miss Clemencia Benítez
Dr. Antonio Ortiz
Dr. Oscar Costa-Mandry.

A delightful day was spent by all and matters pertaining to the College were amply discussed. Dr. Suárez particularly recommended to all members of the College that they make arrangements to be present at the next Annual Session of the College, to be held in New Orleans, March 27 to 31, 1939.

Meetings of the Puerto Rico Chapter of the College have been primarily social occasions, due in part to the great number of medical meetings that are held locally. The Chapter feels the social gatherings better help than purely scientific meetings. In all the scientific meetings held by the various medical organizations in Puerto Rico, members of the College, comprising the Puerto Rico Chapter of the College, take active part.

O. Costa-Mandry, F.A.C.P.

Dr. Manfred Kraemer, F.A.C.P., Newark, N. J., was elected Chairman and Dr. Hyman I. Goldstein (Associate), Camden, was elected Secretary of the Section on Gastroenterology of the Medical Society of New Jersey, at its last annual meeting in Atlantic City during May.

Dr. Thomas Kain, F.A.C.P., Camden, and Dr. John W. Gray, F.A.C.P., Newark, are Secretary and Chairman, respectively, of the Section on Medicine of this Society.

Dr. Ralph E. Porter (Associate), Superintendent of the U. S. Marine Hospital, Fort Stanton, N. M., since 1934, has been appointed Superintendent of the Marine Hospital in Savannah, Ga.

Dr. Henry A. Christian, F.A.C.P., and Dr. Charles Sidney Burwell, F.A.C.P., Boston, were among the chief speakers at the twenty-fifth anniversary celebration of the Peter Bent Brigham Hospital, Boston, May 5 to 7.

Dr. Samuel M. Feinberg, F.A.C.P., Chicago, addressed the Clinton County (Iowa) Medical Society May 5 on "Summer Allergy."

Dr. Andrew C. Ivy, F.A.C.P., Chicago, addressed the Genesee County (Michigan) Medical Society May 4 on "Clinical Aspect of the Physiology of the Gallbladder."

Dr. Karl F. Eschelman, F.A.C.P., Buffalo, has been appointed consultant on firearms identification and ballistics to the Buffalo police department.

Dr. William J. Mallory, F.A.C.P., Washington, D. C., addressed the Cambria County (Pa.) Medical Society at Johnstown, June 9, on "Diagnosis and Management of the Common Diseases and Disturbances of the Digestive Tract."

Dr. Thomas Parran, F.A.C.P., Surgeon General of the U. S. Public Health Service, was a guest speaker at a symposium on syphilis before the Philadelphia (Pa.) County Medical Society on May 11. Among the Philadelphia speakers were Dr. Baldwin L. Keyes, F.A.C.P., and Dr. Daniel J. McCarthy, F.A.C.P.

Dr. M. Herbert Barker (Associate), Chicago, conducted a clinic on cardiovascular diseases and hypertension at the ninth annual meeting of the Ninth Councilor District Medical Society of Wisconsin, in Stevens Point, May 5.

Dr. Herman M. Pollard (Associate) has been promoted to Assistant Professor of Internal Medicine on the faculty of the University of Michigan Medical School.

The sixth annual assembly of the Omaha Mid-West Clinical Society will be held October 24 to 28, 1938, at the Hotel Paxton, Omaha. Dr. Henry L. Bockus, F.A.C.P., Philadelphia, and Dr. O. H. Perry Pepper, F.A.C.P., Philadelphia, will be guest speakers on the subject of medicine.

Dr. Arthur C. Christie, F.A.C.P., Washington, D.C., addressed the Medical Society of the County of Monroe (New York) May 17 on "Modern Trends in Medicine with Special Reference to Hospital Insurance."

Dr. Max Pinner, F.A.C.P., for some years principal diagnostic pathologist, District Tuberculosis Hospitals, New York State Department of Health, has been appointed chief of the division of pulmonary diseases at Montefiore Hospital, New York City, beginning September 1.

Dr. Rufus I. Cole, F.A.C.P., was tendered a testimonial dinner at the Rockefeller Institute for Medical Research recently, at which he was presented with a bound set of reprints from the institute hospital, from which he resigned as director last year.

Dr. William Egbert Robertson, F.A.C.P., Philadelphia, was recently appointed Medical Director of the Northeastern Hospital, Philadelphia.

Dr. B. B. Vincent Lyon, F.A.C.P., has been made Associate Professor of Medicine at Jefferson Medical College of Philadelphia.

Dr. Edgar A. Hines, F.A.C.P., Seneca, has been re-elected secretary-treasurer of the South Carolina Medical Association.

Dr. John A. Kolmer, F.A.C.P., Philadelphia, addressed the Roanoke (Va.) Academy of Medicine recently on "Infection, Immunity and Specific Treatment of Lobar Pneumonia."

The West Virginia State Medical Association held its seventy-first annual meeting at White Sulphur Springs July 11 to 13, under the presidency of Dr. Charles W. Waddell, F.A.C.P., Fairmont. Dr. Louis H. Clerf, F.A.C.P., Philadelphia, was among the guest speakers, his subject dealing with pulmonary suppuration. Dr. Charles B. Chapman (Associate), Welch, delivered the oration on medicine, "Human Blood as a Therapeutic Agent."

Dr. George H. Gehrmann, F.A.C.P., Wilmington, Del., was a guest speaker at the meeting of the West Virginia Industrial Physicians and Surgeons Association, July 10, his subject being, "Industrial Medicine and Toxicology."

Dr. William C. MacCarty, F.A.C.P., Rochester, Minn., addressed the Monroe County (Ind.) Medical Society May 9 at Bloomington on "Cancer and Cancer Control."

Dr. Elmer L. Sevringhaus, F.A.C.P., Madison, Wis., addressed the Shawnee County (Kan.) Medical Society at Topeka on June 6, his subject being "Endocrine Therapy in General Practice."

Dr. Daniel L. Sexton, F.A.C.P., St. Louis, and Dr. Euclid M. Smith, F.A.C.P., Hot Springs National Park, addressed the sixty-ninth annual meeting of the Southwestern Kentucky Medical Association at Paducah recently on "Endocrinology in General Practice" and "Management of the More Common Arthritic Disorders," respectively.

Dr. Maynard E. Holmes, F.A.C.P., has been promoted to Professor of Clinical Medicine at Syracuse University School of Medicine.

Dr. Wingate M. Johnson, F.A.C.P., Winston-Salem, has been elected President of the Board of Trustees of Wake Forest College.

Dr. Robert Bruce Nye (Associate), Philadelphia, director of the Curtis Clinic at Jefferson Medical College Hospital, has been appointed medical director of Jefferson Hospital, succeeding Dr. Henry K. Mohler, F.A.C.P., who has been appointed Dean of the Medical College.

Dr. Rudolph H. Kampmeier, F.A.C.P., has been promoted to Associate Professor of Medicine at Vanderbilt University School of Medicine.

Dr. R. Finley Gayle, Jr., F.A.C.P., Richmond, has been appointed to the State Advisory Board on Mental Hygiene, State of Virginia.

Dr. F. O. Mahony, F.A.C.P., El Dorado, has been elected first vice-president of the Union County (Ark.) Tuberculosis Association.

Dr. William J. Mallory, F.A.C.P., has been installed as President of the Medical Society of the District of Columbia. Dr. Coursen B. Conklin, F.A.C.P., was re-elected Secretary-Treasurer.

Dr. Leon S. Lippincott, F.A.C.P., Vicksburg, Miss., has been elected Secretary-Treasurer of the Mississippi State Hospital Association.

Dr. L. H. Fuson, F.A.C.P., St. Joseph, has been elected a vice president of the Missouri State Medical Association.

Dr. Hillyer Rudisill, F.A.C.P., Charleston, has been elected Secretary-Treasurer of the South Carolina X-Ray Society.

Dr. Edward Clay Mitchell, F.A.C.P., Memphis, Tenn., has been elected Chairman of the Section on Pediatrics of the American Medical Association.

Dr. Bedford Shelmire (Associate), Dallas, Tex., was elected Chairman of the Section on Dermatology of the American Medical Association.

Dr. W. S. Rude, F.A.C.P., Ridgetop, Tenn., has been elected vice president for middle Tennessee of the Tennessee State Medical Association.

Dr. J. W. Preston, F.A.C.P., Roanoke, and Dr. F. H. Smith, F.A.C.P., Abingdon, have been reappointed by the Governor as members of the Medical Examining Board of Virginia for additional terms of four years.

Dr. Robert L. Levy, F.A.C.P., Professor of Clinical Medicine, Columbia University College of Physicians and Surgeons, and Dr. William G. Leaman, F.A.C.P., Associate in Medicine and in charge of the Department of Cardiology, Woman's Medical College of Pennsylvania, will address the Medical Society of the State of Pennsylvania at Scranton in October on "The Therapeutic Aspects of Cardiac Pain" and "The Follow-Up Treatment of the Ambulatory Cardiac," respectively. Dr. Roland N. Klemmer, F.A.C.P., Lancaster, will discuss the pathology of the circulatory system.

Dr. Joseph H. Barach, F.A.C.P. (Pittsburgh, Pa.), addressed the Franklin County Medical Society (Chambersburg, Pa.) on July 19, 1938. In the afternoon his topic was "Underlying Principles and Treatment of Diabetes." In the evening, he delivered an illustrated lecture on his experiences during "A Medical Tour of South America."

AMERICAN COLLEGE OF PHYSICIANS

Geographical Distribution of Members

July 13, 1938

United States	Masters	Fellows	Associates	Total
Alabama		17	10	27
Arizona		26	4	30
Arkansas		18	6	24
California		203	42	245
Colorado		46	20	66
Connecticut		63	24	87
Delaware		7	2	9
District of Columbia		114	42	156
Florida		32	12	44
Georgia		48	33	81
Idaho			4	4
Illinois		123	51	174
Indiana		38	14	52
Iowa		35	9	44
Kansas		18	13	31
Kentucky		37	17	54
Louisiana		47	12	59
Maine		18	4	22
Maryland		69	19	88
Massachusetts		106	35	141
Michigan		139	50	189
Minnesota		100	24	124
Mississippi		14	5	19
Missouri		70	18	88
Montana		11	4	15
Nebraska		35	16	51
Nevada		2	1	3
New Hampshire		5	3	8
New Jersey		79	22	101
New Mexico		10	2	12
New York		389	178	567
North Carolina		55	15	70
North Dakota		6	1	7
Ohio		120	57	177
Oklahoma		33	19	52
Oregon		18	10	28
Pennsylvania	1	246	97	344
Rhode Island		15	12	27
South Carolina		12	9	21
South Dakota		3	4	7
Tennessee		37	15	52
Texas		89	39	128
Utah		4	5	9
Vermont		3	1	4
Virginia		50	17	67
Washington		25	15	40
West Virginia		33	20	53
Wisconsin		47	9	56
Wyoming		2	1	3
U. S. Possessions:				
Canal Zone		10	2	12
Hawaii		11	7	18
Philippine Islands		3	1	4
Puerto Rico		6	11	17
Total (U. S. & Possessions)	1	2747	1063	3811

AMERICAN COLLEGE OF PHYSICIANS—*Continued*

United States	Masters	Fellows	Associates	Total
Canada:				
Alberta		1	1	2
British Columbia		1	1	2
Manitoba		3		3
New Brunswick		4	1	5
Nova Scotia		1		1
Ontario		31	6	37
Quebec	1	17		18
Saskatchewan		1	1	2
Central America		2	2	4
China		5	1	6
England		3		3
Mexico		4		4
Panama		3	1	4
Siam		1		1
Turkey			1	1
Address Unknown		1		1
GRAND TOTAL	2	2825	1078	3905

OBITUARIES

DR. ARTHUR THURSTON NEWCOMB

Dr. Arthur Thurston Newcomb (Fellow and Life Member), aged 67 years, died at his home in Pasadena on July 19. Though Dr. Newcomb had not been in good health for eight or nine years he had been getting about and doing some practice until the last few days before a recurrent heart attack caused his death.

Dr. Newcomb began his practice in Pasadena forty years ago. He tried to bring back new ideas and methods of procedure from his frequent visits to other medical centers and foreign clinics. During the World War he was chief of the medical service at the Base Hospital in San Diego. He held membership in his County, State and the American Medical Associations, the Los Angeles Clinical and Pathological Society, the American Therapeutic Society and many other scientific organizations. Dr. Newcomb was a senior member and one of the founders of the Huntington Memorial Hospital in Pasadena and was long an active member of the University Club. He is survived by his widow, Mrs. Marie M. Newcomb; a son, Arthur Newcomb, Jr., of Pasadena, a sister and two brothers, one of whom is Dr. Ralph Newcomb of Upper Lake, California.

EGERTON CRISPIN, M.D., F.A.C.P.,
Regent, Southern California

DR. JOHN A. McVEAN

Dr. John A. McVean, 59, Lakewood (Ohio) physician, died May 26, 1938, at his residence after an extended illness. Dr. McVean was born in Youngstown, Ohio, and received his M.A. degree from Duquesne University in Pittsburgh in 1899. For several years he was chief chemist at the Hazelton Furnace in Youngstown, now one of the mills of the Republic Steel Corporation. He then decided to follow a doctor's career and was awarded his M.D. degree at Western Reserve Medical School in 1917. For two years Dr. McVean was medical superintendent at City Hospital. He taught pathology for several years at Western Reserve. He was a member of the Cleveland Academy of Medicine and the Lakewood Chamber of Commerce, and was made a Fellow in the American College of Physicians in 1926.

A. B. BROWER, M.D., F.A.C.P.,
Governor for Ohio

DR. PHILIP B. MATZ

Dr. Philip B. Matz (Fellow, 1927), Chief of the Medical Research Subdivision of the Veterans' Administration, Washington, D. C., died suddenly June 25, 1938, at Santa Monica, California. The cause of death was coronary disease.

Dr. Matz left Washington June 1 for a two-month tour of Veterans' Administration hospitals throughout the country. He had just concluded a series of round-table conferences on tuberculosis in connection with the annual meetings of the American Academy of Tuberculosis Physicians and the National Tuberculosis Association. He had also read a paper on "The Incidence of Primary Bronchiogenic Carcinoma" before the Section on Pathology and Physiology of the American Medical Association.

Born in Baltimore, Maryland, August 25, 1885, Dr. Matz received his early education in the schools of that city and New York. He held the degree of Lit.B. from Mather College, Kansas City University, Kansas City, Kansas, and M.D. from Long Island College of Medicine, Brooklyn, New York (1908). In addition he did postgraduate work at Kansas University, St. Louis University, Chicago University, Rockefeller Institute for Medical Research, New York City, and Michael Reese and Cook County Hospitals, Chicago, Ill.

Dr. Matz entered the government service in 1909 when he was appointed Assistant Surgeon, National Military Home, Leavenworth, Kans., and assigned as Chief of Laboratory. His government service was continuous from that date except for the four-year period 1914–1917, during which time he conducted private laboratories in Kansas City and Leavenworth, Kans., and served as consultant serologist at the Federal Penitentiary, Leavenworth, Kans.

In August 1917, Dr. Matz was commissioned 1st Lt. M.C., U. S. Army, and assigned to active duty as Chief of Laboratory Service, Base Hospital, Camp Travis, Texas. He was promoted to Captain in February 1918 and continued as Chief of Laboratory Service. A report of his intensive work during the influenza epidemic of 1918 may be found in an article entitled "Laboratory Studies in Influenza at Camp Travis, Texas," published in the *American Journal of the Medical Sciences,* November 1919.

After the war Dr. Matz was commissioned as Surgeon (Reserve), U. S. Public Health Service, and served as Chief of the Laboratory Service at U. S. Public Health Service Hospitals, Dansville, N. Y., Ft. McHenry, Md., Maywood, Ill., Camp Logan, Texas, and Legion, Texas. His successful record as pathologist in the field organization of the Veterans' Administration and his active interest in research work led to his appointment in August 1925 to the position of Chief of Medical Research in Central Office, which he held continuously until the time of his death. In supervising medical research in the 81 hospitals and 22 dispensaries operated by the Veterans' Administration, Dr. Matz was particularly interested in the various diseases found in the ex-service men. He was the author of numerous studies in serology, cardiology and other circulatory diseases, tuberculosis, arthritis, cancer, diabetes mellitus, silicosis, etc. In 1926 he was appointed a member of a special Board convened by the Government to study the residuals of warfare gassing.

He belonged to many medical societies including the American Medical Association, the American College of Physicians, the American Society of Clinical Pathologists, the American Academy of Tuberculosis Physicians, the Kansas State Medical Society, and the Clinical Club of Washington. He was also a member of the American Legion and the Military Order of the World War, the Torch Club of Washington, and the Sojourners Lodge No. 51.

Dr. Matz was a man of great charm, a soldier with a most enviable record, a physician of exceeding skill, and a writer of rare ability. He was embued with an unselfish spirit of devotion to duty. His numerous friends in and out of the Veterans' Administration will miss him sadly and in his passing the medical profession at large has lost one of its most valued associates. While there are many salient points with respect to his honored career, it is difficult in a life so full of accomplishments to choose for particular commendation any one achievement.

Dr. Matz is survived by his widow, Mrs. Eleanor Crampton Matz; his mother; three brothers; and three sisters.

He was buried with full military honors in the National Homes Cemetery, Fort Leavenworth, Kansas, Thursday, June 30, 1938.

CHARLES M. GIFFITH, M.D., F.A.C.P.,
Washington, D. C.

DR. RALSTON LATTIMORE

Dr. Ralston Lattimore, Savannah, Ga., aged 67, died on April 20, 1938, at his home after a long illness. He was a native of Savannah. Dr. Lattimore attended the Savannah High School and Moreland Park Military Academy and received the degree of doctor of medicine from Columbia University College of Physicians and Surgeons in 1893. For three years after graduation he served as house physician at Mount Sinai Hospital in New York, then for a year he was active physician at the Sloan Maternity Hospital. Later he took special postgraduate work in Berlin and Vienna and then began the active practice of medicine in Savannah. Dr. Lattimore had always been associated with organized medicine and held many honorary offices. He was author of the Vital Statistics Bill, which was passed by the Georgia Legislature in 1915 while he was chairman of the Committee on Public Policy and Legislation for the Medical Association of Georgia; the Medical Practice Bill was passed while he was President of the Georgia State Medical Association, 1913–14. He was a member of the Medical Association of Georgia, Southern Medical Association, American Medical Association and a Fellow of the American College of Physicians since 1921.

GLENVILLE GIDDINGS, M.D., F.A.C.P.,
Governor for Georgia

DR. GEORGE EMILE NEUHAUS

George Emile Neuhaus (Fellow) was born in Berlin, Germany, in 1866 and died in Omaha, Nebraska, on May 15, 1938.

He was educated at Bellevue Hospital Medical College where he received his M.D. degree in 1891. He had postgraduate study at the Harvard University Medical School, Boston Psychiatric Institute and the Neurological Institute of New York. He practiced first in New York, leaving there to become Medical Director of the Mount Airy Sanatorium at Denver, Colorado, from 1907 to 1922, and locating in Omaha, Nebraska, in 1922.

Dr. Neuhaus, at the time of his death, was Associate Professor of neuropsychiatry at Creighton University School of Medicine, and Attending Neurologist at St. Catherine's Lutheran and St. Joseph's Hospitals. He was a member of the Douglas County Medical Society, Nebraska State Medical Association, American Medical Association, American Psychiatric Association, Central Neuropsychiatric Society, Midwest Clinical Society and a Fellow of American College of Physicians since 1920.

Dr. Neuhaus was an earnest student with broad and unlimited interests in his chosen field. He was a kind and wise counsellor and his death is a great loss both to the medical profession and to the community.

WARREN THOMPSON, M.D., F.A.C.P.,
Governor for Nebraska

DR. FREDERICK LEONARD FENNO

Dr. Fenno of New Orleans, Louisiana, aged 43, died suddenly on July 20, 1938. In the passing of Dr. Fenno the medical profession of the City of New Orleans and the State of Louisiana has lost one of its most brilliant and popular members and the American College of Physicians has lost one of its most useful and enthusiastic Fellows.

Dr. Fenno was born at Plainfield, New Jersey, in 1895. He attended public schools in Plainfield, New Jersey, and in New Orleans, Louisiana. He received his M.D. degree from Tulane University of Louisiana School of Medicine in 1917. He has served as instructor in Clinical Neurology in Tulane University of Louisiana School of Medicine. He was a member of the Orleans Parrish Medical Society, Louisiana State Medical Society, Southern Medical Association, American Medical Association, American Public Health Association and the American Association of School Physicians. He had been a Fellow of the American College of Physicians since 1928. In his earlier experience he served as assisting consulting neurologist at the Eye, Ear, Nose and Throat Hospital and the Illinois Central Railroad Hospital of New Orleans; and he was senior visiting neurologist of the Charity Hospital and was medical director of the Orleans Parrish Public Schools.

For years Dr. Fenno had devoted himself to the practice and teaching of neurology, his chosen specialty, and many of the younger practitioners of the South have heard with sorrow and regret of the untimely death of their former teacher.

He was very popular with the members of the Orleans Parrish Medical Society, who, recognizing his ability as an organizer and executive, selected him as Chairman of the Entertainment Committee for the next annual meeting of the College which is to be held in New Orleans.

Dr. Fenno was a pleasing and affable type of personality and was loved and admired by his many friends.

He was public spirited and active in civic and social affairs and his untimely passing leaves a void in the hearts not only of the medical profession, but of the public whom he served.

JOSEPH E. KNIGHTON, M.D., F.A.C.P.,
Governor for Louisiana